

Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 41

**Peter R. Martin: Recollections of the History of
Neuropsychopharmacology Through Interviews Conducted by:**

Volume 1. Thomas A. Ban (2014)

Volume 2. Leo E. Hollister

Volume 3. William E. Bunney

Volume 1

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**RECOLLECTIONS OF THE HISTORY OF
NEUROPSYCHOPHARMACOLOGY THROUGH INTERVIEWS
CONDUCTED BY THOMAS A. BAN**

Edited by

Peter R. Martin



Thomas A. Ban (1986)

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PREFACE

This volume is a compendium of interviews conducted by Thomas A. Ban as part of an important historical project undertaken by members of the American College of Neuropsychopharmacology (ACNP) at the close of the twentieth century. Thomas Ban was the driving force and the primary editor of a ten volume treatise¹ recording biographical interviews of neuropsychopharmacologists under the aegis of ACNP to preserve for future generations the experiences of those who pioneered the field. Ban was primary interviewer for a staggering 56² of the 235 interviews in this series, conducted by a team of 66 interviewers. The Ban conducted interviews provide an unusual insight into the field by virtue of the number and diversity of neuropharmacologists he interviewed. The resulting volume of re-edited Ban interviews assembles in archival form what may be viewed as another of the many important contributions of Ban to the fields of psychiatry and neuropsychopharmacology - communicating his wide understanding of how the forms of mental illnesses manifest and are influenced by neuropsychopharmacologic agents. To offer the reader the opportunity to hear Ban's own voice, two interviews of Ban himself, conducted by Leo Hollister (December 9, 1996) and William E. Bunney, Jr. (December 10, 2007) are included to complete this volume.

¹ Ban TA (Editor). *An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews.* (Volumes 1-10). Brentwood: American College of Neuropsychopharmacology. 2011.

² The edited transcripts of the 56 interviews Thomas Ban conducted were first presented in the following volumes of the Oral History series: Samuel Gershon, Charles Jelleff Carr, Robert A. Cohen, and Alfred M. Freedman in Volume One – Starting Up, edited by Edward Shorter; Philip B. Bradley, Enoch Callaway III, Turan M. Itil, Ernest Hartmann, Philip S. Holzman, and Louis Sokoloff, and A. Arthur Sugarman in Volume Two–Neurophysiology, edited by Max Fink; Hans Christian Fibiger, Kjell G. Fuxe, Leslie L. Iversen, Murray E. Jarvik, Joseph Knoll, Irwin J. Kopin, Steven Marc Paul, Alfred Pletscher, and Richard J. Wurtman in Volume Three – Neuropharmacology, edited by Fridolin Sulser; Donald M. Gallant, George Gardos, Burton J. Goldstein, John M. Kane, John E. Overall, Eugene S. Paykel, Frederic Quitkin, Alan F. Schatzberg, and Nina R. Schooler, in Volume Four – Psychopharmacology, edited by Jerome Levine; William E. Bunney, Jr., William T. Carpenter, Jr., John F. Greden, Gregory F. Oxenkrug, Robert M. Post, William Z. Potter, Elliott Richelson, and Daniel P. van Kammen in Volume Five – Neuropsychopharmacology, edited by Samuel Gershon; Herbert Barry, III, Kanellos D. Charalampous, and Charles R. Schuster in Volume Six – Addictions, edited by Herbert Kleber; Thomas N. Chase, Paula J. Clayton, Thomas B. Cooper, David L. Dunner, Burr S. Eichelman, Alexander H. Glassman, Katherine A. Halmi, Dilip V. Jeste, Seymour Kaufman, William T. McKinney, Eric M. Shooter, Myrna M. Weissman, and Paul H. Wender in Volume Seven – Special Areas, edited by Barry Blackwell; George R. Heninger, Stephen H. Koslow, Paul Leber, and Charles B. Nemeroff, in Volume 8 – Diverse Topics, edited by Carl Salzman; Frank M. Berger, Jonathan O. Cole, Louis A Gottschalk, Leo E. Hollister, Conan Kornetsky, and George M. Simpson in Volume 9 – Update, edited by Barry Blackwell; and Frank J. Ayd, Jr. and Martin M. Katz in Volume 10 – History of the ACNP, edited by Martin M. Katz. The text of the interviews in this volume is based on text in those ten volumes. Yet, because of further editing, the interviews in this volume are not identical to the interviews in the “oral history” series.

This Preface is not intended to summarize, nor can it do justice to Tom Ban's long and productive career. To help the reader better understand the scope of Ban's academic life and his many contributions to the field of neuropsychopharmacology, I have included an abridged version of Ban's curriculum vitae (Appendix 1) and an outline of his major scientific contributions (Appendix 2). My goal for this Preface is to provide a personal glimpse of Tom as mirrored in our friendship of more than three decades.

I first met Tom Ban, in May 1984, in Nashville, while Mike Ebert was recruiting me to join the faculty of the Department of Psychiatry at Vanderbilt University School of Medicine. Tom had recently returned to Vanderbilt from a two year period in Geneva at the World Health Organization and was just settling into his final years in Nashville prior to retirement, in Toronto. Our initial conversation soon established that we had very similar life histories, and even though we had never formally met before this evening in Nashville, we might well have crossed paths many, many times before, without knowing so.

Tom and I were born in Budapest 20 years apart, both of us the only child of middle class parents. I felt quite comfortable in Tom's presence, almost at once. I knew a great deal about Tom's early life and found that it overlapped substantially and sometimes involved acquaintances shared with my parents, as Tom was only a few years younger than they were.

Tom enrolled in the Medical University of Budapest, which in 1969 was renamed Semmelweis University. This was not an easy decision for Tom; at age sixteen, he had been awarded a prize in a national student literary competition for an essay he wrote on the transformation of the 19th century novel in the early 20th century, attributing this change to the influence of Freud and psychoanalysis. Thus, although Tom felt particularly well prepared for a career in literature, history, and philosophy, previously honed survival skills remained a profound influence, as Tom relates in his interview with Bunney (*this Volume*), "But, my world that had collapsed with World War II was changing again. Hungary became a "people's democracy," and I thought it would be safer to enter medical school." This was not an unusual decision in post-war Hungary. In my own life, I heard that my father, despite a fine singing voice, eschewed his dreams for a life in the opera for the more "secure" profession of engineering. Tom commenced psychiatric training at the National Institute of Nervous and Mental Disorders, in Budapest, laying the

groundwork for a long and productive career studying mental diseases and their treatment by using psychoactive drugs.

Ban immigrated to Canada (Montreal), as did I with my parents (Toronto), during the Hungarian Revolution of 1956. He obtained licensure to practice his profession in a new homeland, which required re-training as an intern in Halifax and as a psychiatrist in Montreal. Interestingly, he completed his internship training contemporaneously with another Hungarian physician, who subsequently became a good friend of my parents, as well as our family physician, many years later, in Toronto. Ban had the good fortune to settle in Montreal at McGill University. When in the early 1960's we moved to Montreal for my father's job, my family lived for a number of years in an apartment building, which, I later understood from Tom, was directly across the street from Tom's father's residence and around the corner from Tom's own house. So, until the 70's, we were neighbors, both commuting to McGill via essentially the same route without knowing it.

Ban's first McGill mentor was the eminent neurosurgeon, Wilder Penfield, who offered Tom a fellowship for which he applied while in Vienna, the first stop in the world outside of Hungary. After returning from his internship in Halifax, he trained in psychiatry with Heinz Lehmann, his teacher and long term collaborator, and then, Ewan Cameron. I never met Ewan Cameron; although I had heard of the "notoriety" associated with research he conducted for the United States government intelligence establishment, which Tom tells me was quite overblown. One summer in medical school, I worked in a laboratory at the Montreal Neurological Institute right next door to Wilder Penfield's office, and had the occasion to exchange pleasantries with "the Great Man" in the hallway; and of course, I was honored to participate in a lecture to the first year McGill medical class by Heinz Lehmann, in 1971, which was impressive, indeed.

During the McGill period, Tom published *Conditioning and Psychiatry* (Aldine 1964), his first book, based on his diploma thesis, in which he adopted the view that the conditional reflex is the elementary unit of mental functioning in the brain. After integrating information on conditioning at the behavioral and neurophysiological level, he began to study conditional reflex variables in psychiatric patients. This was to provide a means for bridging the pathologies in the processing of signals in the brain, which he perceived as the essence of mental illness, with the mode of action of psychoactive drugs as outlined in a volume he wrote in collaboration with Heinz Lehman, *Experimental Approaches to Psychiatric Diagnosis* (Charles C. Thomas 1971). He also

wrote *Psychopharmacology* (Williams and Wilkins 1969), in which he aimed to set a foundation for what was to become translational neuropsychopharmacology; by examining to what extent structure-activity relationships with psychoactive drugs translate into neurochemistry, neurophysiology, and behavioral and clinical effects. This book brings to mind another overlap in our lives - Tom gave a complimentary copy of this book to his dentist, who just happened to be a good friend's father; when I entered medical school, my friend's father proudly showed me this book and I remember being very impressed that a "fellow Hungarian" was so accomplished. This was a particularly productive period for Tom and he published extensively (Appendix 1), including an incredible one to two books most years. Tom's career flourished at McGill; he founded the first Division of Psychopharmacology in a university setting and directed the first WHO training program in psychopharmacology.

He was recruited to Vanderbilt University and the Tennessee Neuropsychiatric Institute, in 1976, by Marc Hollender and Fridolin Sulser. At Vanderbilt, Tom continued his involvement with international neuropsychopharmacology, which he began at McGill; this culminated in his position as Consultant in the Division of Mental Health at the World Health Organization in Geneva, Switzerland for two years, in the early 1980s. This appointment seems to have been a significant watershed in his career, both professionally and personally - Tom and his family loved living in cosmopolitan Geneva, and thus, the seeds were sown for their eventual departure from Nashville as well as Tom's shift in scientific focus. Although in *Psychopharmacology* he recognized that the pharmacological heterogeneity within psychiatric diagnoses precludes meaningful biological research of mental illness and the discriminative use of psychotropic drugs, only after his return from Geneva, did he begin developing methodologies that he believed could break the impasse created by studying pharmacologically heterogeneous populations.

My friendship with Tom began within a very short time after I arrived at Vanderbilt, in 1986 (see in the front piece of this *Volume* a portrait of Tom from this period). We would sit for hours and talk about many things, especially his vision of psychiatry. I soon realized how magnificent and orderly a mind he possessed. It was apparent that he could expound at length on almost any area of psychiatry raised for discussion - he had been there before, had thought about it profoundly, and probably had published a paper or two, or even a book, on the topic. Most impressive to me was how he could direct you to the exact publication that was the first in which the particular topic was raised, as well as the historical procession of the concepts involved. Thus,

I would simply listen and learn (perhaps as I did when editing this volume), and more often than not, found his insights invaluable. Newly arrived from the National Institutes of Health, I was charged with establishing the Division of Alcohol and Substance Abuse within the Department of Psychiatry at Vanderbilt, still greatly influenced by the unique research style practiced in Bethesda, which began and ended in the laboratory. Tom, however, firmly believed that psychiatry, regardless of whether it is considered a branch of neuroscience, is a clinical discipline with its own methodology, in which psychopathological symptoms express most directly the pathology in the processing of signals/experiences in the brain, and only nosological entities can completely represent the totality of their clinical manifestations from onset to outcome of the illness.

It was at this time that Tom was finalizing the *Prolegomenon to the Clinical Prerequisite* (Pergamon Press 1987). This publication began the process of developing a *Composite Diagnostic Evaluation (CODE)* system for psychiatric disorders (JM Productions 1989). Tom half-seriously viewed this work as a first step for creating “codes” for the processing of mental events, as in the “genetic code,” hence his choice of the acronym. At the time, I thought he was much *too* focused on his perspective without seeing all the excitement in genetics and neuroscience that, of course, captivated me. He confidently held that the finest genetic study designed to understand the molecular complexities of the dysfunctional brain of a psychiatric population would fail without a strong anchor in diagnosis, or at least in a pharmacologically homogeneous population. He strongly believed that in the study of mental illness, psychiatry should guide, rather than follow neuroscience and that psychotropic drug development was wandering lost in the desert without psychiatric feedback. His advice to me was, “Peter, you need to see more patients.” This was not the wisdom I wanted to hear from my friend, quite the opposite of what my other colleagues advised me - they viewed clinical work in psychiatry as a distraction from real scientific accomplishment (“protected” time for research was their mantra).

In fact, only during the last decade have I recognized how greatly influenced I was by Tom’s counsel, and that it may have pointed me in the right direction. Could the cause of this have been that he was living a very parallel life just 20 years ahead of my own?

Tom “retired,” in the mid-1990s, to Toronto, a city which has been a wonderful choice for him and his family. My parents also relocated to Toronto and while they were still living, I had the occasion to visit Toronto often and to see Tom. More recently, Tom and I have sustained our friendship with regular phone calls and via other electronic means. Retirement for Tom has not

reduced his devotion to his scholarly activities and he works harder now than do many who are half his age. He retired from Vanderbilt, so that he could dedicate his full time to collaborate with his former fellows to develop and use CODE-related diagnostic systems in the re-evaluation of psychotropic drugs already in clinical use and in the clinical development of new psychotropics. During Tom's retirement, other subjects that have captivated his interest have been how, in the absence of a valid psychiatric nosology, the corporate world has influenced the development of pharmacotherapy in psychiatry, and how to most appropriately conceptualize conflict of interest in neuropsychopharmacology. Another vitally important theme in Tom's scholarly life during the Toronto years that I alluded to in the beginning of this Preface is his passion for the history of psychiatry, especially neuropsychopharmacology. The fruits of this passion and tenacity are two historical multi-volume treatises, *The History of Psychopharmacology and the CINP, As Told in Autobiography* (edited with D. Healy and E. Shorter; Animula 1998-2004) and *An Oral History of Neuropsychopharmacology* (American College of Neuropsychopharmacology 2011) and other related volumes (Appendix 1).

Most recently, Tom has spearheaded the establishment of the International Network for the History of Neuropsychopharmacology (INHN). Once again, he has recognized an emerging problem for neuropsychopharmacology. The flood of information with possible relevance to mental illness generated by rapid advances in the neurosciences in cyberspace has become a distraction. Yet, he also recognized that the same advanced communication technology that rendered these isolated bits of information so readily accessible without scrutiny could be employed to undo the harm by organizing the information into an historical and proper psychiatric context, and thereby useful for the study and treatment of mental illness. By doing so, Tom believes that INHN could provide a bridge not only between different generations of clinicians and scientists involved in neuropsychopharmacology but also between the different disciplines involved in the field.

The contextual guidance Tom provided has been invaluable to me introducing this volume. I believe this compendium of interviews conducted by Tom Ban will serve to depict the man and his journey, in addition to those of whom he interviewed.

In closing, I would like to sincerely thank Ronnie D. Wilkins, Ed.D., CAE, the Executive Director of the American College of Neuropsychopharmacology, for allowing me to edit and

assemble this volume of the interviews conducted by Thomas A. Ban, which were initially published under the imprimatur of the American College of Neuropsychopharmacology.

Peter R. Martin

Nashville, Tennessee, U.S.A.

June 25, 2014

1. FRANK J. AYD, Jr.

TB: This will be an interview with Dr. Frank Ayd, Jr.³, one of the pioneers of neuropsychopharmacology for the Archives of the American College of Neuropsychopharmacology. We are in Washington, DC, at the Biltmore InterContinental Hotel. It is July 19, 2001. I am Thomas Ban.

TB: Frank, we've known each other for a long time.

FA: That's correct.

TB: I've followed your work since I started my residency in psychiatry at McGill in the late 1950s. What I would like to do now is go through your life and achievements. Let's start from the very beginning. Tell us where you were born, brought up, and something about your education and early interests.

FA: Well, Tom, I was born in Baltimore, Maryland, and I'm the son of a doctor. I had two doctors before me in our family. My father was a doctor, and my grandfather, who was first a pharmacist, but later, became a physician. He was very interested in pharmacology. My father, originally, was a general practitioner, but ultimately, became a pediatrician and was fairly well known for his work in that area. My father had quite an influence on me. He was a very kind, soft-spoken man.

I became an avid reader, partly from his example, and by his encouragement.

I'm the oldest of five children. I have a brother, who became a Jesuit Priest, and as a Jesuit, ultimately, became president of one of the Jesuit schools and universities in Pennsylvania. I have another brother, who became an assistant to the mayor of the city of Baltimore. I have two sisters, who married and had families; they're in the real estate business. So, you get an idea of the family. It's a strong family. We all see each other fairly regularly, because we all live in Baltimore. I went to grammar school, a Catholic grammar school, in Baltimore, a Jesuit high school in Baltimore, and a Jesuit college in Baltimore. I also went to medical school in Baltimore. So, every bit of my education was in the city of Baltimore. I graduated from the University of Maryland when World War II was on. And, when I graduated from medical school, I, like all graduates, was

³ Frank J. Ayd, Jr. was born in Baltimore, Maryland in 1920 and graduated in 1945 with his M.D. from the University of Maryland. From 1955, he was chief of psychiatry at Franklin Square Hospital in Baltimore. He was also director of education at Taylor Manor Hospital in Ellicott City, Maryland, and president of Ayd's Communications. He died in 2008. He was interviewed in Washington, DC on July 19, 2001.

given time, before called on active duty, to get some training in medicine. So I did an internship in a Catholic hospital in the city of Baltimore. And, when I finished that internship, I had applied for a residency in pediatrics. Now, you see my father's influence, his example. And, the Navy gave me time to do all these before I started on active duty.

TB: Can we go back a little?

FA: Sure.

TB: What year did you enter college?

FA: Let's see. I entered Loyola College, in 1938, in Baltimore.

TB: What did you major in?

FA: Well, actually, I took a Bachelor of Arts degree, after I took science courses in biology and chemistry. At that time, I was not sure about whether I was ever going to go to medical school. I just wasn't sure, then. Truthfully, I was toying with the idea that I might become a Jesuit Priest, and it was not an easy decision to make. I did make it, anyway.

TB: What made you decide to enter medical school?

FA: Well, I guess, in part, it was the example of my father and the other doctors I had met through my father. I also had a conviction that I didn't have a real vocation for the priesthood; that has proven to be correct. I made my decision while at a Jesuit retreat house, with my class, before graduation. The retreat conductor or master was a priest from England, a very well-known British philosopher. He looked somewhat like my concept of Ichabod Crane, physically. And, he started that retreat with an opening statement, which I have never forgotten. The statement was, "Gentlemen, there are two things in this world, God and yourself. Everything else is extraneous matter to be used by you for your salvation or your condemnation." That was his opening remark of a two and a half day meditation on what your vocation would be. That convinced me that I really didn't have a religious vocation. It was good for me. So, I immediately applied for medical school. The war was on. They needed more doctors. So, I was admitted.

TB: By the time you entered medical school you were married, weren't you?

FA: My wife was a freshman a year after me, when I was a sophomore. And, I fell in love with her and she fell in love with me and we got married after two and a half years, because we couldn't get any time off from school. And that was the beginning of the marriage that has lasted now fifty-seven, going on fifty-eight years. As you well know, it has been a very fruitful marriage; there are

twelve children. We now have thirty-two grandchildren and sixteen great grandchildren and two more on the way. And, we are all still staying together. Raising those kids, educating them was a challenge; to work hard, get the money to pay tuitions, and everything else. But, I have no regrets about that.

TB: I saw somewhere that you were active in the student body, while in College. Is this correct?

FA: Oh, yes. I was very active in the student body and became, in my senior year, the president of the student council at Loyola. That got me involved in the relationship between students and faculty and gave me some training in negotiating. It was worth the time and effort I put into it.

TB: Then, after College you entered medical school.

FA: Yes, I got to medical school.

TB: When did you graduate from medical school?

FA: 1945.

TB: And, what did you do after graduation?

FA: Well, I did my internship in St. Joseph's Hospital, and then, I started my pediatric residency at the University of Maryland's university hospital. But then, I was called up to active duty, because they needed more men. Initially, I was assigned to surgery in the Bethesda Naval Hospital. It was a big mistake; I have no manual dexterity, whatsoever. And, I said, "Oh, my Lord." Fortunately, the commanding officer of the hospital was Admiral Hogan, who was Catholic. I'd met him on retreats down at the retreat house of the Jesuits, so I had no hesitancy going to his office and asking if I could see him. It was my first real introduction to how the military protects their big officers when his secretary said, "Well, who are you"? And, I said who I was. And she said, "Well, I don't know. The Admiral is pretty busy. I don't know if he'd have time to see you or not." And, I said, "Well, just tell him it is Frank Ayd from Loyola." She, begrudgingly, said "all right." About fifteen minutes later, she came out and said, "Follow me." I went into Admiral Hogan's office, and, we exchanged greetings. Then, he said, "What's your problem?" And after I told him, he said, "Well, we don't have any pediatric services in the Navy right now. We have, what some people might call babies, but those are psychiatric patients." Then, he said, "I'm going to send you up to Bainbridge." Bainbridge was a naval base very close to the VA Hospital at Perry Point that was understaffed. This was at the time when the nationwide program started in which doctors were being sent to military bases and then loaned by the army or by the Navy to VA hospitals. It was a great experience, Tom, because there were about two

thousand psychiatric patients and only eight doctors in the whole hospital that included the superintendent, the assistant superintendent, an internist, a surgeon, a dentist and a radiologist. So, you could figure out, that left two “psychiatrists” to take care of the psychiatric patients. You were pretty much on your own but you were given every opportunity to learn and practice. When I went there, Tom, to be perfectly honest, I had no ambition to become a psychiatrist. But, after six months there, I began to realize that there’s something very intriguing about psychiatric patients. Let me give you one of my experiences. It was a bitter cold winter night, and as you might know, Perry Point chucks out into the Chesapeake Bay. I was the officer of the day and I got a call from someone from one of the wards, telling me that a patient had escaped from the shower. My immediate response was, “I wouldn’t worry about him. It’s so damn cold. He’ll be back in another fifteen minutes.” All of those attendants, actually, were farmers and when they couldn’t farm, they worked at the hospital. And, he said, “Doc, you don’t know these people. If we don’t find him, he’s going to be an icicle.” So, we started the search and found him. He was pretty blue and pretty hypothermic, but he revived and that was it. He could have died. And, you would think that the pain that was caused by the cold would make him come indoors. It didn’t. So, I began to wonder about what makes these people so different. TB: It was a real learning experience, much more than anyone could convey in a class. FA: Oh, yes. I had another patient who stuffed himself with newspapers and then ignited the papers. I got called over, and when I arrived, he was just sitting there responding to his hallucinations, and was not complaining of any pain or anything else. He had, I guess, twenty percent of his body badly burned; second and third degree burns. And, I didn’t have to give him opioids or anything else for pain. He never complained of pain. So, I learned that schizophrenics have decreased pain sensitivity. That was for me a very important observation. So, I began to become extremely interested in schizophrenia.

TB: Did you decide by that time that you would become a psychiatrist?

FA: Yes, I did decide by that time.

TB: Can you remember the different treatments you used in those days?

FA: Oh, yes. Bromide was still used; and we had patients get bromism from being overdosed with bromides. Barbiturates were used a lot. Paraldehyde was also used a lot. I hated the smell of it. We used, in those days, insulin, as well. We had our share of fatalities with insulin. If you had experience with insulin coma therapy, you know that you have to be extremely careful because you can easily induce severe, perhaps, irreversible hypoglycemia.

TB: So, you became involved in treating psychiatric patients with drugs and insulin coma?

FA: That's right. And then, of course, I got involved with ECT. I tell you, Tom I was convinced that ECT was a great treatment. When I was doing my internship, I had seen some patients who got ECT and I saw the kind of "awakening" that Oliver Sachs described with LDOPA in Parkinsonism after three or four treatments with ECT. And, at Perry Point, I seized the opportunity to get experience at administering ECT.

TB: Was ECT at the time still administered without muscle relaxants?

FA: What you needed was a couple of strong men to hold the patient down, and a very firm pad under the back to arch it, to reduce the risk of spinal compression. You also needed a rubber mouthpiece to keep the cheeks from being damaged or the jaw dislocated. We didn't have, at the time, a safe, short acting barbiturate that could rapidly induce anesthesia. That was introduced after I was out of Perry Point. I was already in practice when I was asked by a company to take a look at an IV anesthetic, which they said, on the basis of animal studies, was of short duration and rapidly induced anesthesia. It was sodium barbital. I administered it to a series of patients prior to ECT, and it seemed to work.

TB: Are we talking about the early 1950s?

FA: That's correct, yes.

TB: What did you do after Perry Point?

FA: Well, Tom, by this time, I had children. I had to get out and get more money than the Navy was paying me. That was for sure. To increase my income, I went into practice. But it takes a couple of years to start a practice; to become known by your colleagues and get referrals. So, I also had some GI Bill of Rights funding for education I could capitalize on. So, I went back to the University of Maryland. It happened that I very much liked John Kranz, the pharmacologist there. And I took the course John Wagner, a pathologist, was offering in neuropathology. It was a one-year course, and I used to go down to attend the course during the day and see patients in my office at nights.

TB: So, by 1951, you had opened your practice?

FA: That's correct.

TB: Did you also have an academic appointment?

FA: Oh, yes. Even while I was at Perry Point, I taught psychology at the Catholic University in Washington, DC. Then, my alma mater also asked me if I would head up a small department in psychology. And I did that for about two or three years, I think, until they got a full time man with a Ph.D. in clinical psychology.

TB: Didn't you present your first paper in those years?

FA: Yes, it was around that time. My first paper in a medical journal was my first report on chlorpromazine. I presented it at the Southern Medical Association's annual meeting, which happened to be in St. Louis that year. It was the first paper on chlorpromazine in this country, presented at a national meeting.

TB: Didn't you publish a couple of articles prior to your paper on chlorpromazine?

FA: Oh, yes. I had already published before in one of those throwaway magazines. They were commentaries, on topics, as for example, "The Lack of Pain Sensitivity in Schizophrenics," and things of that sort.

TB: Didn't you get involved in the care of psychiatric patients in a general hospital setting in those years?

FA: Oh yes, absolutely.

TB: Weren't you one of the first in the United States who practiced psychiatry in a general hospital setting?

FA: That's correct, Tom. That is correct. And again, I was very fortunate that the first hospital, a general hospital, that allowed me to have psychiatric patients admitted to my service, was St. Joseph's in Baltimore, where I had done my internship. My father had been on the staff at that hospital, I don't know for how many years, he was probably there for forty years. So, the nuns were very gracious, and the chief of medicine, of course, trained me during my rotating internship. And I started doing ECT there and admitting inpatients. That was feasible. In those early days when chlorpromazine came along, I had to train the nurses and the interns, and also, had to educate everybody that psychiatric patients are not as dangerous as people might think they are. It worked. There was only one suicide I had over ten years on my service at St. Joseph's, Bon Secour's, St. Agnes' and Mercy Hospitals. All these were Catholic hospitals, where I had admitting privileges. And, one also learns fast. I had a patient, a very cunning patient, whom I had on suicide watch. I had a nurse assigned to the patient to watch her constantly. Well, when it was quiet on the ward,

as night began to set in, she asked for a drink of water. The nurse gave it to her, and then, she dropped the glass on the floor. The nurse went out to get a mop. When she came back in, the woman had gone out the window, and she died. Most of the patients who were admitted were depressed patients, who were not seriously suicidal. If they were, we had extra precautions taken for them. Many of them, I gave ECT, because I was convinced of the value of ECT, particularly, in suicidal patients.

TB: So, you used ECT extensively? Weren't you a member of an ECT Society in those years?

FA: Oh, yes. It was called the Electroshock Research Association. It had many very fine people, whom I met in that Association. Lothar Kalinowsky and David Impastato from New York, Howard Fabing from Cincinnati, George Ulett from St. Louis. I, actually, went to Howard Fabing and Doug Goldman, in Cincinnati, to spend with them a week. As you know, Doug Goldman, was a board certified internist, psychiatrist, and electroencephalographer. These were wonderful people to be literally tutored by. I'd stayed in their home; they opened their door and welcomed me in. So did Lothar Kalinowsky, who couldn't have been kinder to me.

TB: So, you were taught ECT by Kalinowsky?

FA: Oh, yes. I watched him and he taught me different techniques with respect to electrode placement, and so on.

TB: I suppose this happened before he wrote his classic text on ECT.

FA: Yes, a few years before that. It became clear to me that administration of a muscle relaxant was very desirable, because you could avoid fractures. And it was also clear that it was preferable to administer it with a short acting rapidly metabolized anesthetic. As I mentioned it before, I did a clinical study with sodium barbital before, and I presented the results of that study at an annual meeting of the Electroshock Research Association. It was well received. I got one of the two prizes of the Association for my paper.

TB: How did you get to the idea of giving a muscle a relaxant prior to ECT?

FA: Well, I had met A.E. Bennett at an APA meeting, in San Francisco, and we ended up becoming friends. He had just started his pioneering work with succinylcholine, around that time, and I watched him administer the substance a couple of times. He had me do it under his supervision. It was marvelous to see how it worked. If you gave it too quickly, the patient would stop breathing on you, and that could be frightening. So you have to be very prudent in the

administration of it. But, it mixed very well with barbital sodium. It focused my attention on drug-drug interactions, because if you didn't do it right, instead of helping, you could harm the patient and scare yourself. That's for sure. I felt it was important that patients get this combined treatment prior to being given ECT. I took sort of an interest in this treatment and went out and talked and wrote about it.

TB: How did you get involved in psychopharmacology?

FA: Well, I was in private practice, OK? And, in private practice, you make a commitment to a patient that you are going to provide the best possible care you can provide that alleviate their suffering that is so concomitant with psychiatric disorders. We had a definite effective treatment for depressed patient in ECT. So, I thought if we could use succinylcholine with barbiturates, we could make ECT an even safer treatment. As it was, why not to try other drugs in the treatment of psychiatric patients? It so happened, that a Squibb representative, who used to call on my father, came to see me. I was using my father's office at the time, because I didn't have enough money coming in to pay the rent for somebody else's office. We started chatting, and he asked me what I was doing. I told him what I was doing, and about my interest in using medication in treatment. So, a couple of weeks later, I got a phone call from Squibb, from a doctor at Squibb, who wanted to come down to see me. That sounded interesting. He came to see me with a product he called mephenesin that had muscle relaxing properties. He was looking for someone who would be willing to explore it, as a possibility of using it as an anxiolytic, muscle relaxant, in the treatment of neurosis. So, I thought, well that sounds interesting. And after reading the information on the animal data they had, I found that it looked reasonably safe; I said, OK. I did a study with the substance and found that it was practically a dud. It had some sedative properties but did nothing really to alleviate the kind of tension that the severely ill psychiatric patient has. So, I gave a narrative report on my findings to the company that was never published. They told me, right off the bat that based on my report, plus of one other person's report, they had decided that there was no market for this compound. But, that identified me as someone who is interested in working with new drugs. It's amazing how the word gets around in the industry. And, the next drug that I ever agreed to do a study on was chlorpromazine. I got a phone call from a Dr. Bill Long. Bill Long's Jesuit brother was a principal at the high school that I attended, and he mentioned to Bill Long my interest in drugs. And Bill called me that he had a drug from Rhône-Poulenc in Paris,

and he would like to talk to me about it. So, he came to Baltimore, and I'll never forget it, he had samples of 10 mg tablets of chlorpromazine with him. You'd have to give a full bottle to get some effects from it. But, I tried the drug, and initially, had some unhappy experiences with it. The first patient, to whom I gave chlorpromazine, was in a general hospital. He was a very tense, obsessive-compulsive guy. I put him on a relatively low dose, but still, in two days, he got jaundice. The nurses called and said, "Your patient is yellow." I went in to see him right away. I was never convinced that chlorpromazine, actually, was responsible for his jaundice because when we admitted him to the hospital for his obsessive compulsive disorder, he, also, had fever and some malaise. So, we just withdrew the chlorpromazine and waited until the storm blew over. It cleared up spontaneously. But then, I had a patient, whom I had been seeing for about two years, and ten days after I put her on chlorpromazine, when she came back to my office, Tom, she was as jaundiced as she could be.

So, I said, "Oh, Mary, how long have you been like this?" And, she said, "Oh, it's almost ten days, doctor." I said, "You stopped the medicine, didn't you?" And she replied, "Oh, no, no, it's helping me, and you've been so kind trying to help me, I just kept taking it." I learned one thing right off that you don't necessarily have to discontinue chlorpromazine when a patient gets jaundiced. In fact, I kept her on it because she had some very imminent relief. I had known her for long enough that I could see definite changes in her condition. And, she agreed to continue on the medication. The family also agreed. We never altered the dose, and the jaundice went away. She continued to improve, and then, finally, the chlorpromazine was stopped.

TB: So, you got your chlorpromazine directly from Rhône Poulenc. Most investigators in the United States got it from Smith, Kline & French. It seems that the first patients you treated with chlorpromazine were not schizophrenics.

FA: They weren't. You don't see that many schizophrenics in private practice. I had at the time just gotten admitting privileges at Taylor Manor hospital, a private psychiatric hospital.

Most of the private patients don't go to be treated in private hospitals for schizophrenia, unless they are very wealthy, because they would need to stay there a long time. Most of the patients admitted to private hospitals are bipolar, hypomanic or manic patients. Schizophrenic patients are admitted mainly for a short time to control their agitation and aggressive behavior, or that sort of thing.

TB: When was your first paper on chlorpromazine published?

FA: It was in 1955.

TB: By the time you published your paper on chlorpromazine, you probably started your studies with reserpine?

FA: Yes.

TB: Where did you get the reserpine from?

FA: I got it from CIBA.

TB: From CIBA?

FA: Yes.

TB: By that time, of course, they knew that you were interested in drugs?

FA: Oh, yes, yes. I'm trying to think, now, who contacted me first. I believe it was Jack Saunders. But it could have been someone else from the medical department of CIBA. Saunders, ultimately, left them, and went to Rockland State Hospital to work with Nathan Kline. Reserpine was not as dramatic a drug as chlorpromazine. It took time to take effect. It, also, frequently caused unpleasant side effects, gastrointestinal disturbances, vomiting, and so forth. Many patients just wouldn't take it, consistently. Yet, if you had a patient, who tolerated it and took it faithfully, it was very definitely a positive drug. It was nowhere near as positive as chlorpromazine, in terms of antipsychotic effects.

TB: You were among the few who reported on both, chlorpromazine and reserpine. You might have been the only one in the USA who reported on both.

FA: Nate Kline had reported on both as well. So did Al Kurland at Spring Grove State Hospital, in Baltimore. Al did a study on chlorpromazine about the same time I was doing mine, but he did not get on the program in St. Louis, where the first chlorpromazine studies in the United States were discussed. And then, outside of Maryland, Doug Goldman was doing a study with chlorpromazine in Cincinnati. As a matter of fact, Doug attended the meeting in St. Louis, and in a discussion of my paper, he got up and asked me if I had encountered any agranulocytosis with the drug. And I said, "No, I've heard that that it occurred in Europe, but I've not had any trouble with it." It turned out that he had two cases. I had some patients who developed agranulocytosis on chlorpromazine, as time went on. Doug was a very astute observer. TB: You were among the first to publish on chlorpromazine in North America. The first, I think, was Heinz Lehmann.

FA: Yes, it was Heinz's paper from Canada that was the first, and subsequently, I presented my paper. Then, a paper was published in the JAMA. It was written by someone in Texas, I can't remember his name now. He got published first, but my presentation preceded his publication. And, of course, Fritz Freyhan, at Delaware State Hospital, and Bertrum Schiele were working with the drug also. In a very short period of time, there were many people working with chlorpromazine. It really exploded.

TB: There were much less people involved with reserpine than with chlorpromazine. FA: Very few people did much with reserpine, because there was a big controversy over whether or not it produces depression. I mean, there were lots of people who did become depressed on reserpine, but this didn't alarm me because I was never sure that it was really drug induced. In my office, of course, I was concerned whether it would be safe to give ECT to depressed patients whose hypertension was treated with reserpine. That's when I called on Lothar Kalinowsky and David Impastato in New York, and Leo Alexander in Boston. What became evident to me was that depression often carries with it hypertension, and as soon as the depression goes away, the hypertension disappears without any particular treatment for it. As a matter of fact, I did a follow up study on a large number of patients, who allegedly had reserpine induced depression and the follow up showed that there was no substance to that. There were many people who took reserpine as a prophylactic medication, even though they were well, and did not become depressed again. There was a long hiatus after they stopped taking reserpine before their next depression started. So, they were having cyclic episodes of depression. On the other hand, if the patient is vulnerable to depression, it's possible that reserpine could bring vulnerability for depression to a reality. The results of treatment with reserpine were not sufficiently good to justify the risk of using it. So, it fell by the wayside, as you know. However, it's still on the market after fifty years as an antihypertensive. And, if you look into the data, it did not cause an unusually high incidence of depression among the people who were treated with it. So, it's not a bad drug, but it's not a desirable drug.

TB: Did you use yourself reserpine in low doses in hypertensive patients in your practice?

FA: Yes, and it worked. I never had any problem with depression in my patients treated with reserpine.

TB: You used to report adverse effects with psychotropic drugs before anyone else but had no trouble with reserpine. .

FA: Correct. Nate Kline gave me the name, “Dr. Side Effect.”

TB: Oh, did he?

FA: Instead of “Dear Friend,” he used to write me, “Dear Side Effect, I’ve just read your latest report. Is that all you’ve got to do is to look for side effects?”

TB: You published a couple of reports on the side effects of chlorpromazine?

FA: Yes. I reported on jaundice with chlorpromazine. I also reported on the gastrointestinal and vascular side effects of reserpine.

TB: I think you also reported on fever in chlorpromazine treated patients.

FA: Oh, yes. I tried to report, honestly, everything I saw. In fairness to the patients, you have to make these things known, so the other doctors can say, “Look, there is a risk with this,” and get their informed consent for treatment.

TB: You also reported on generalized hypersensitivity to chlorpromazine.

FA: And, of course, I reported very early on extrapyramidal symptoms with the drug. I had one patient, a young woman with bipolar disorder, who was put on chlorpromazine for her euphoria, agitation and irritability, and developed a very acute dystonic reaction. I filmed her. You can’t convince people about some of these reactions, without showing them. I filmed this patient and sent my film to Smith Kline & French. They looked at it and sent it to their consultants, but none of them had seen this reaction before. They got all kinds of opinions that it was hysteria, some kind of toxicity, and what not. And then, Smith Kline arranged for me to go to the annual meeting of The American Academy of Neurology in Atlantic City, and to present the film there to a committee of five expert neurologists. They agreed that it was a dyskinetic reaction, but they didn’t know what caused it. But, even after that many people thought that it was a hysterical reaction in a neurotic woman.

TB: In the late 1950s, in addition to your practice, were you not also the acting director of a psychiatric service in a general hospital?

FA: Yes, I became Chief of Psychiatry at Franklin Square Hospital.

TB: Your work in those years was recognized nationally.

FA: I think that’s correct.

TB: You received a distinguished service award....

FA: Oh, yes, I had gotten that.

TB: You were recognized as the Outstanding Young Man of the Year.

FA: Yes. Well, it so happened, that I was nominated for it. It started with a newspaper report after a presentation I had made in Atlantic City at an APA meeting. The Associated Press covered the event. Then, the executive director of the Mental Health Society in the United States, a former newspaper man from Oklahoma, contacted Nate Kline, Henry Brill, and me about testifying in Washington at a congressional hearing on psychiatric illnesses and their treatment. I agreed, and the three of us went to Washington and testified. I got a lot of publicity because I took the position that if one wants to save money in patient care, one would need to use chlorpromazine. I pointed out that successful use of chlorpromazine costs so many cents a day, whereas untreated illness costs so many dollars more a day. I also made a plea for the coordination of activities in drug treatment. I felt that the government should collect, analyze, and summarize the data on drug treatment and the findings should be taken into consideration in handling the problems of the psychiatrically ill. We do that for diabetics and we do that for epileptics. Why can't we do it for psychiatric patients? To make a long story short, they appropriated the money that was needed for the establishment of the Psychopharmacology Service Center. And then, Jonathan Cole was appointed as the first director of PSC.

TB: You had been involved in studying many drugs including methylphenidate. Could you tell us something about your research with them?

FA: Well, in so far as methylphenidate is concerned, my dad was a pediatrician, and like all pediatricians, he had his share of ADHD kids. And he did what most pediatrician did, treated them either with a sedative drug, like liquid diphenhydramine, or methylphenidate. Regarding diphenhydramine, I often wondered how much of its effect was due to its alcohol content, and how much was due to the sedative effects of the drug. Insofar as methylphenidate was concerned, I was contacted because people knew that I was interested in working with drugs, and also because they thought that I could get patients from my father. So, I did a study with methylphenidate and showed that it was effective not only in children and adolescents, but also, in some adults. As you know, there are adults who have ADHD. I had some among my patients. In appropriate doses, methylphenidate is clearly an effective drug, even if not for all, but for a substantial proportion of ADHD patients.

TB: Did it create for you any problem in working with children?

FA: You know I did a residency in pediatrics.

TB: Yes.

FA: And beside that I also saw pediatric patients with my father. He did house calls. He was a real old time family doctor, who was a specialist in pediatrics. And then, I saw my share. When I started to work with methylphenidate, I had no trouble getting patients, because a lot of the pediatric guys in town knew me as a resident in pediatrics, before the Navy called me up. And, I just called a couple of them and said, "You know, I need some patients and there will be no charge for the medication and for my service." Well, you know what that meant; I got a lot of referrals. It didn't take very long to see that methylphenidate helps. I also recognized soon that it has less risk for abuse and dependency than amphetamines. I became very convinced about that. You might remember, some years later; I think you were with WHO at that time, Sweden raised concerns about the dangers of methylphenidate. I remember the meeting held in Geneva that dealt with the Swedish concerns. Leo Hollister was there, representing the United States, along with, I think Sid Cohen.

TB: Yes. Then you also did some research with meprobamate, in the 1950s.

FA: Yes, I did. I used meprobamate primarily in epileptic children. I was asked to study whether meprobamate has anticonvulsant effects. So I did a study and found that it has some anticonvulsant effects in epileptic children. The seizure rate would go down, but it would depend on the type of seizures the kid had. It was not a very potent drug for severe and frequent grand mal seizures, but for minor epileptic episodes, it could be beneficial. I say, could be, because some of these children can go for weeks without having a darn thing even if they're taking a placebo. Meprobamate so, in my judgment, is an effective drug and has helped lots of people. I'm not talking now just about epileptics; I'm talking about people with anxiety states or co-morbid anxiety, and so on; it would alleviate anxiety. Unfortunately, dependency on meprobamate became a real problem because doctors used it like candy. You can't do that with the kind of drug that meprobamate is. The limitations of meprobamate became more and more apparent with the advent of chlordiazepoxide. When Librium (chlordiazepoxide) was released for clinical use, it was quite clear that it would be a real competitor of Milltown (meprobamate). Nevertheless, my first paper on chlordiazepoxide

was a report on my negative findings with the drug, although it was effective in controlling some of the symptoms of my patients.

TB: So you had a practice that allowed you to study drugs in all kinds of psychiatric populations.

FA: Yes, I had a practice in psychiatry that was kind of a general practice in psychiatry. I had some training in pediatrics, so I wasn't too concerned about children. I also had enough sense to know if something was out of my area of expertise.

TB: There were very few people in those years studying drugs in children.

FA: That's true. There were very, very few people doing it, very, very few. I never identified myself, deliberately, as a psychopharmacologist in pediatrics; although, I've done my share of it and I'm still doing some work in children.

TB: And, you also did some early work with perphenazine in the aged, right?

FA: Oh, yes, yes, that's right. My first paper on perphenazine was on its value in the elderly. Perphenazine was an interesting compound. So, was thioridazine, which on a milligram for milligram basis was a very weak drug, but it didn't cause much extrapyramidal signs. It is not true that it is totally free of EPS. If you gave the right dose, you could make patients stiff as a board. So, on the other hand, chlorpromazine had more sedative effects than thioridazine, caused more EPS, weight gain, and hypotension. And what was the difference between those two drugs? It was a difference in the structure of the side chain. Thioridazine was introduced before perphenazine. Another phenothiazine introduced before perphenazine was Compazine, a very good antipsychotic drug.

TB: Prochlorperazine?

FA: Yes, prochlorperazine.

TB: In Canada, it was available as Stemetil.

FA: Stemetil, that's right. So, at any rate, then along came perphenazine. It had all the assets of chlorpromazine but did not have as much anticholinergic and sedative effects. Unless you gave a fairly high dose, you didn't get much in the way of EPS and so on. It looked as a substance that is going to be a good drug for the elderly, because you're not going to get the cardiovascular side effects that you would get with the other phenothiazines available at the time. And, it was compatible with medications that elderly people took for co-morbid medical illnesses, such as diabetes, hypertension, cardiovascular disease, etc. After doing the original work, I suggested to

Schering, the company that had perphenazine, that we put together a team to study it. And with their authorization, I put together the team. I called Nate Kline, and got him involved, and I got also Bert Schiele involved. It was the three of us. I gathered enough data for submission to the FDA. Then we had a meeting in New York and we presented all the data we had. Perphenazine differed from the other phenothiazines by its side chain and became a very widely used drug. But still, it didn't have quite the kick for the schizophrenic patient or the severe manic. So, that led chemists to twist things further around, and with a fluoride atom added, to synthesize fluphenazine.

TB: So, you were much aware of structure activity relationships and tried to translate even minor molecular changes into clinical effects.

FA: Right. And, I gave a paper at the 1st CINP congress in Rome on Structure Activity Relationships with Antipsychotics. I covered twenty-three different antipsychotic drugs.

TB: Did you work with all available phenothiazines for clinical studies at the time?

FA: Oh, yes, with all the available ones that could be studied.

TB: In 1956, you went overseas to visit some European centers in psychopharmacology.

How was that arranged?

FA: There were seminars organized by European pharmaceutical companies, like May & Baker in England, Rhône Poulenc in France, and CIBA, Geigy, Roche, and Sandoz in Switzerland and they invited experts from the USA to participate. I was invited to meet, also, with their personnel and I met with personnel from each one of the companies. These were pharmacologists, physicians, who were dealing with other doctors and getting them involved in clinical investigations and what not. We were advising them as to possible clinical applications of compounds based on animal data. I was convinced, Tom, that there was a dire need for better communications between psychiatrists in the world, not just in the United States. You were in Canada. You know, that sometimes, what you call schizophrenia would have been called mania in the United States or vice versa. And, as a matter of fact, there was a study done involving patients in London and in New York, which showed that there was good reason for saying that this is a problem. And, in the course of having lunch with these people at these different companies, I brought up this concern of mine. There has to be some kind of an international organization so that when a guy in Switzerland says, "This is schizophrenia," and presents his criteria, it's comparable to the criteria that we might be using in Baltimore, Maryland, and so forth.

Because, to read an article that says, this drug is good for schizophrenia, to me, meant nothing, because there were no real criteria for the diagnosis of schizophrenia. After I finished my stay in Europe, I came back home, and subsequently, I got a phone call from Switzerland about having a symposium in Milan, to discuss the possibility of establishing a college in the field. I was honored for being invited and I attended it. It was a very good meeting. Out of that meeting came the CINP.

TB: So this symposium took place about a year after you returned from your trip in Europe attending seminars organized by drug companies? Am I correct?

FA: You are correct.

TB: You already met on your first trip many people from different European centers.

FA: That's correct. I got to know, pretty much, the leading people in Europe.

TB: Can you mention a few by name?

FA: Well, Paul Kielholz, Jules Angst, and many others. I talked with these people, had dinner with them; so, I was learning about what they did and returned home optimistic about what was going on.

TB: If I remember correctly, you went to Milan, on your second trip to Europe, with your family.

FA: We went to Rome, first.

TB: You went to Rome, first?

FA: That's correct.

TB: Could you tell us more about that second trip?

FA: Yes, I'm proud of it, Tom. When the invitation came for the Milan meeting, I realized that the date of the symposium was just around the time when one of my daughters, Theresa, was supposed to have her First Holy Communion. So, I told my wife, Rita, "I don't know whether I can accept the invitation." Then I got a date for the Holy Communion that did not conflict and I accepted the invitation to attend. Well, that was in the fall, and this was to be the next spring. On Christmas Eve, the pastor of my parish had a heart attack and died. So, my wife said, "What are we going to do?" I said, "We'll wait until the new pastor is appointed and see what happens." So, the new pastor was appointed and I went down to see him and asked him when he thought the First Holy Communion was going to be and he said, "Don't ask me. I don't expect to be here more than six weeks. I'm a temporary pastor, as far as the Cardinal, or the Archbishop is concerned." Sure enough, about six weeks later, the new pastor was officially appointed. I went down to see

him and he was going to change nothing, so the Holy Communion was going to be on a date that would conflict with the symposium. So, after I came home and told that to my wife, she asked, "What are you going to do?" I said, "I'm going to write a letter to the Holy Father." She said, "What are you going to do that for?" And, I said, "Well, he's the Bishop of Rome and he would be the one who would have to authorize her First Holy Communion in Rome." So, my wife said, "You think he's going to answer?" I said, "All he can do is say, 'No.'" Well, weeks go by and no answer and it is Holy Week, now it is three weeks before the meeting in Milan. I was in Los Angeles addressing pediatricians on the use of psychotropic drugs for behavior disturbances in children, when I was handed a message, "urgent call, call your wife immediately." So, I stopped the lecture and went out and called my wife and she said, "We've heard from the Pope." We should be in Rome on Good Friday. This was the Tuesday before, and I was in Los Angeles. And I said to her, "Meet me in New York. I'll change my ticket and we'll go over." We arrived there, Good Friday, as requested. And, of course, you don't do anything on Good Friday, but Holy Saturday morning, we went to the Vatican. I presented the credentials that had been sent over by the Apostolic Delegate from the Swiss guards, and we met the man from the Secretary of State's office, who is now one of my closest friends, and he told us of the arrangements. Now, that the Pope agreed to my daughter making her First Holy Communion in Rome, we are to be his guests for a week. For Easter Sunday, we had special seats up in the left cannonade there, and our daughter was to make her First Holy Communion, on Wednesday. It would be in St. Peter's, at the altar of St. Pius X, who's the patron saint of first communicants, and mass would be held by the Carmelite Fathers, since Theresa was a Carmelite. Everything was carefully thought out. Before the First Communion, we were to have an audience with Pius XII, but the night before, we got a phone call from his secretary saying, "Have to cancel for tomorrow, because Prince Rainier and Grace Kelly are coming." And, of course, heads of states are given priority. So, we were brushed aside. Two days later, we, then, had a proud audience with Pius XII and he gave my daughter his zucchetto, his little white hat. He had tremendous interest in medicine, Tom. He wrote more on medicine than any Pope in the history of the Church. And, I told him I was going to Milan, and wanted this First Holy Communion, in Rome. And so, he was interested in what's this meeting about in Milan, and I told him. Well, he said, "Once over, let me know what's happened." So, I said, "OK." So, before we got to Milan, we got an invitation to his birthday party. We had a great time. And the next day, we got off to Milan for the meeting. I'm human,

Tom. To me, that was the most exciting thing that had ever happened to me, and obviously, I told people about it.

TB: So, you went from the Pope to the psychopharmacology symposium, organized by Garattini that led to the founding of the CINP. But wasn't there also another meeting, independent of the one in Milan, where the need for an international organization was discussed?

FA: Well, yes, there was one that was supported by CIBA. The one organized by Garattini was a scientific symposium where I gave a paper on the Use of Antidepressants in Children.

TB: Can you tell us something about the other meeting, the one sponsored by CIBA?

FA: It was organized by people in Europe, who were active in the field of psychopharmacology Paul Kielholz played a big role in it. I don't know whether Jules Angst was there. I think he was, but I'm not sure. And the professor from Vienna, what is his name, was also there.

TB: Hans Hoff.

FA: Yes, Hans Hoff, from Vienna.

TB: What about Otto Arnold?

FA: Yes, Arnold was there.

TB: Frank Fish?

FA: Yes, Frank Fish from Liverpool was there.

TB: Michael Sheppard?

FA: Oh, yes, Mike Shepherd was there. Many of the leading psychiatrists of Europe were there. Still, it was not a scientific meeting, but a meeting to discuss whether to have an organization that would set up standards in the new field, etc, a kind of organization as the ACNP, here, is now. It was decided that there is a need for such an organization and, what is his name, was asked to help setting it up.

TB: Ernst Rothlin?

FA: Yes, Rothlin. There was then, another, meeting that was held in Switzerland during the time of a congress...

TA: The 2nd World Congress of Psychiatry.

FA: That's it. You got it. The founding meeting of the CINP was held in a restaurant at the railroad station.

TB: The dinner, at the Zurich railway station, was organized by Rothlin. He hand-picked a number of people and invited them to attend.

FA: Exactly. I give a major paper at the Congress, and attended Kuhn's historical paper on imipramine, but was not invited.

TB: Did you attend Nate Kline's psychopharmacology symposium at the Congress?

FA: Yes. People, by that time, were beginning to realize that we could not go ahead in a haphazard way any longer in psychopharmacology. It was worse than the Tower of Babel. And that was not good.

TB: So, you participated in the 2nd World Congress of Psychiatry, in 1957, listened to Kuhn's first paper on imipramine, and attended Nate Kline's symposium at the Congress, but were not invited to attend the founding meeting of CINP.

FA: And, Heinz Lehmann, Fritz Freyhan, Doug Goldman were not invited either.

TB: But then you attended the 1st Congress of the CINP in Rome.

FA: Oh, absolutely, in Rome.

TB: I'm sure you remember, very well, the meeting in Rome, because it had important...

FA: Well, it was very important because the Pope addressed the Congress, and, in a sense, strongly endorsed psychopharmacotherapy. He strongly endorsed the concept that psychiatric patients are ill. That mental illness is not imaginary, etc. To have a world leader, with his influence, say these things was very, very important.

TB: How did the Pope get invited? Did you have anything to do with that?

FA: How did he get invited?

TB: Yes, how did he get invited?

FA: Exactly who invited him, I don't know, because I was not at that meeting in Switzerland at the railroad station, you see. However, I knew he was going to address the Congress because I had my own contacts at the Vatican. The Holy Father had a policy of writing his own speeches. He seldom used a speechwriter. He was a very educated man. To a certain extent, he had some obsessive features. And, I was asked to provide reprints of some of the better articles in the field, so that he would have a picture of what psychopharmacotherapy was all about. I provided those. He wrote his paper. He gave his paper in French. So, I couldn't follow him very well, but it didn't take more than a couple of hours to have an English translation. After that, I saw the Holy Father

a couple of times. At one of my audiences with him, he asked me if I'd be interested in working at the Vatican. And I asked, "What am I going to do as a psychiatrist there?" To make a long story short, the answer was, "Well, I want the Vatican to be looked upon as a place that knows what's going on in the medical world, in the scientific world, that people see that we are not sitting up somewhere. I would like you to teach for us; we have the Vatican radio, and you could broadcast on the Vatican radio." So, I said, "Well, your Holiness, you know, my wife and I are expecting another child." He said, "I understand. You talk to your wife and let me know what your decision is." So, I prayed about it, talked about it, and made a decision that I would take the job. Now, it was not a full time job, in the sense of ten hours a day or anything like that. The programs were taped often in advance. And so, classes were set up. I taught on Mondays and sometimes on Wednesdays. Then, I would leave Thursday and Friday and go off to anywhere from Sweden to Greece, Turkey, and what not. I still had a lot of expenses to take care of, and I was, also, invited to lecture at almost every medical school in Europe, Tom.

TB: Weren't you also a professor at the University of the Vatican?

FA: Yes, I was the first layman appointed to the faculty of the Pontifical Gregorian University in Rome. The University was founded 400 or 500 years ago by Pope Gregory, and that's why it's named Gregorian University. The students there come from all over the world. There are seventy-two languages spoken, including the different dialects, in the student body. It's quite a place. The students are either ordained priests working on getting their doctorate in Canon Law or Moral Theology, or seminarians, personally selected by their Bishop, who pays their tuition, pays their travel, and their room and board. You get the best education and it costs you nothing.

And, they are very carefully selected. They're men with a vocation.

TB: What did you teach?

FA: I taught two courses. One was called Modern Medical Moral Problems, and the other one was Pastoral Psychology. Now, the men, getting their doctorate in Canon Law, for example, are basically becoming religious lawyers. OK, they're going to uphold the law of the Church and so forth. For example, the Vatican has a marriage court, so that people who want to have their vows annulled can appeal to their Bishop, and from their Bishop, their appeal can go on to Rome, and the marriage court reviews all the data and they make a decision. Obviously, the question is often, was the person capable of making a valid contract? And so, what are the criteria for a valid

contract, whether it's marriage or whatever? So, that was basically the kind of thing that I had taught.

TB: So, this is how you got involved in law?

FA: Yes.

TB: Didn't you get a doctorate in law later on?

FA: I have four honorary Doctor of Law and one honorary Doctor of Science degree.

TB: Is this how you got the one in law?

FA: That's right. I don't think anybody would have given me an honorary doctor in law before I started doing this work. The whole issue, Tom, was that these men needed to know, pretty much, what psychiatry was thinking about in certain areas. As you know, in the United States, for example, there were conflicts between psychoanalysts, represented by a known Catholic priest, who protested a sermon by the Bishop, and complained to the Cardinal. What happened was that the guy said to the Cardinal that he wanted the Bishop to stop what he was doing or otherwise he was going to leave. Now, the rumor is, that at that point, the Cardinal said, "I just accepted your resignation." And, these were the kinds of things. I was, also, there at a time when the Vatican Council was going on, and I ended up consulting to Council Fathers on issues that interested them. The purpose, Tom, of the Vatican radio program was to let the world know that the Vatican is keeping abreast of developments in medicine. For example, on the 100th anniversary of the Red Cross, I did four 15 minutes programs on the history of the Red Cross. At the end of each program, listeners were urged to make a donation to the Red Cross.

During that period, the United Nations put out a series of postage stamps for the world to unite "against malaria." Every member of the United Nation countries issued a postage stamp for the world to unite "against malaria," and I was asked to do a series of programs on malaria. I'll never forget that, Tom, when Father Thomas O'Donnell, an Irish priest, who was head of the Vatican radio, called me into his office and said, "Frank, I want you to do four programs on malaria." I said, "Father, that's impossible. I know a mosquito is involved and I know that we can treat it with a few things, but that's about all; I could say it in five minutes." He says, "You're going to do four fifteen minute programs." That's the way he managed it. So that turned out to be a Godsend for me, because I had to go looking into the history of it. Surprisingly, the American library had nothing in their bookshelves that was worth anything on the subject, but in the British

library, I came across a book written by a British historian that was called “The Fever Bark Tree” that was a story of quinine and how the Jesuits brought it back from South America to Rome. Of course, in that period of history, malaria was very common in Rome and threatened many people on the Vatican Council and many religious men. It was an interesting and very informative book. These are the kinds of things that I learned from that book. Thomas Sydenham gave quinine to a couple of members of a family who had fever, thinking that it was, perhaps, malaria. Well, they never got any better. He wrote the most scathing denunciation of the drug that I’ve ever read in my life. He really blistered it, you know. At the time I was in the Vatican, the birth control issue was on. People from Planned Parenthood were lobbying at the Vatican Council, and there were a great number of press people there. Well, as a member of the American Association of Science Writers, I had my press credentials and was able to attend a good number of cocktail parties and ended up becoming involved in birth control. I wrote a book on oral contraceptives, in which I showed that’s it’s really not a contraceptive, but a pill that aborts the fetus. Since the Pope had to make a decision about what is going to be the official position of the Catholic Church in that matter, prominent obstetricians and psychiatrists, including Lopez-Ibor from Madrid, were consulted.

TB: Lopez-Ibor?

FA: He was one of the psychiatrists. There were a couple of psychiatrists from England. But anyhow, the Church didn’t sit back doing nothing. They did something, and as you know, the Encyclical was finally publicized. I served on a committee for that, along with a Jesuit theologian from Massachusetts, a lady theologian from Maryland, and another well-known Jesuit, whose brother is a well-known internist in the United States, who spent his priestly life focused on medical moral problems. The four of us were on a committee, reviewing and commenting, “This is good; this is not quite clear, and what not.” In a sense we were proofreaders or peer reviewers. It was very educational. So, I can tell you one thing, which is the absolute truth, I was never bored in the three years I was there.

TB: You were also involved in publishing a journal.

FA: Well, it was not a journal; it was a newsletter.

TB: Newsletter?

FA: Medical Moral Newsletter.

TB: But wasn't there also a Magazine?

FA: Oh, yes, but I didn't start that. I wrote articles for the Magazine of the Palatine Fathers, a religious group that started in Italy and are now all over the world.

TB: So, you started the Medical Moral Newsletter.

FA: Yes, the Medical Moral Newsletter.

TB: That was in 1964, right?

FA: That's correct.

TB: And, I think you continued with it until quite recently.

FA: That's correct. About three years ago, I stopped it. I got to the point I couldn't handle it.

TB: Could you tell us something about that newsletter?

FA: Well, it was, originally called The Medical Moral Newsletter for Religious. You know, there were so many changes going on from heart transplants to in vitro fertilization. In fact, right now, stem cell research is becoming the "in thing" in this country and believe me there are many theologians looking into that. Well, anyway. I started that because, in the interval, between sessions of the Council, the priests would go back to their diocese, and some of them asked me to keep them informed if anything comes up in the medical field while they were away. And, I said "sure." So, I sort of started sending them mimeographed information. And, they liked it very much. So, I thought, well, why don't I just start this The Medical Moral Newsletter for Religious? Many dioceses bought it for their archives or for a library that they would maintain for priests. Surprisingly, I had a number of divinity schools and seminaries from various religious denominations, the Protestants, the Episcopalians and so forth that bought subscriptions. And, I covered everything you would want to cover in that kind of thing. I liked to write something stimulating, occasionally. I did an issue on the intrauterine devices, how they work, and on the first page, I had all the different devices. Some of them looked like the Bishop's cruiser. And, that got a big sale. It was a very enjoyable life. It was great for my family. I brought my wife and the twelve kids over to the Vatican and we all went over on the same plane. We were the first family that was that size to fly on the same plane across the Atlantic. Pan Am arranged for all kinds of photographs taken of us, leaving Baltimore, arriving in Italy and so forth.

TB: Were all the twelve kids born between the mid-1940s and the end of the 1950s?

FA: Yes, the youngest was three years old at the time we arrived. I carried her around on my shoulder most of the time.

TB: We talked about the birth of the CINP. We talked about your life in the Vatican. We also talked about the congressional hearings in the United States, which led to the establishment of the Psychopharmacology Service Center, but we have not talked yet about the founding of the ACNP, an organization you had been involved with very much.

FA: I was very much involved in the founding of the ACNP. The idea came from Ted Rothman, who was instrumental in organizing the first meeting. He was a psychoanalyst and not a psychopharmacologist, but he was seeing patients who were given all these drugs and felt that there was a need for knowing a little bit more about them. I'll give you an illustration how some psychanalysts felt about the new drugs in those years. At the New York Academy of Sciences, I gave a paper on chlorpromazine and my experiences with it. The discussant of my paper was a past president of APA, who used to be at Yale. He thought that my paper was very erudite, interesting, and informative. And, then, he got to the punch line, and said, "I have one word of advice to you people in the audience. Hurry up and prescribe this stuff while it still works." At any rate, the idea behind the founding of ACNP was to get better communication between psychiatrists, pharmacologists, industry, and physicians, in general. I played a role, also, in the founding of the British College of Psychopharmacology. It was acknowledged in one of the books of David Healy.

TB: It's interesting that Rothman, a psychoanalyst, was the one who got the idea of founding a society that was to become ACNP.

FA: Rothman had a very good relationship with the medical director of Geigy, and he got those people to put up the money to pay for the travel and foot the bills for the hotel and meals of the organizing group, at a weekend meeting. From the very beginning, there were a few psychopharmacologists involved. Nate Kline was there; I was there; Heinz Lehmann was there; and other leaders in the field. But we had very few pharmacologists, and I thought that we should have more of them. So, lo and behold, at the next meeting, we had Brodie there. What a mind that man had! At that time, he was working on determining the presence of drugs in plasma and serum, and he told us, "We've got to work on determining drugs in the blood because otherwise we don't know whether the drug is in the body." He championed that area of research, and we established

a sub-committee that consisted of Jonathan Cole, Brodie, and myself that focused on that issue. So, before long, we were getting into such issues as hormonal kinetics and pharmacokinetics, and so on. And that, to me, was the important thing. The College should be a College, a source of information, a source of stimulation. That was my position.

TB: During those years, you had been intensively involved in educational activities, weren't you?

FA: Yes, I was.

TB: You made a film, sometimes in the late 1950's, on physical therapies?

FA: Well, I did a couple of films, Tom. I think the one you may be referring to was the series on Medical Horizons. It was sponsored by CIBA Pharmaceuticals and was on prime time television on Sundays. It covered, initially, medicine and surgery, and not psychiatry. All the programs came from hospitals. I was contacted by CIBA to do a program on psychiatry because they didn't want to be criticized for boycotting psychiatry. But, they also had run into people who told them, "No, you can't do this on television because of confidentiality and so on." A physician from CIBA came to Baltimore to see me and we talked it over. I thought it will be a wonderful opportunity to educate the public, so I agreed to do it out of my office. Now, my wife will tell you, she didn't think that was a good idea, mainly because they had to set up all the equipment in the living room. My office was a wing of my house. And, we had the children running around, you know. And the kids always brought their friends in. Actually, to do it, they had us build a special tower about a mile and a half up the road, on a hill, so they could beam it off better. And, they had all this equipment and the kids were just fascinated. But we ended up that the whole front of my house had to be redone after the program was over. My office had punched holes in the wall to get the cameras and little microphones through. I had no idea how much was involved in a national TV show. They had these huge trucks in my driveway to beam the stuff up to the tower on the hill, which beamed it out to the rest of the United States. I had, beside myself, two psychologists working for me, then. I had also two trained internists, who had interest in psychiatry, and two psychiatrists working part-time for me. In one segment, we had the mother interviewed first, and then, the child, then, the psychologist giving the child some tests and so forth. Then, I had a big job, doing the first ECT on television anywhere in the world. And, that took some courage, because, first of all, I had to give the patient some succinylcholine.

Well, that's, as you know, tricky. I did it deliberately, in an elderly patient, because elderly people were not considered to be good candidates for ECT. Then, of course, I used amobarbital sodium to induce anesthesia. The patient was interviewed before treatment, and then again before going home, to show that it can be done in the office. And finally, we had a patient who had had a lobotomy; a very intelligent, attractive woman, who came in and talked to the neurosurgeon. The neurosurgeon explained how it was done, and so forth and so on. Then there was an interview with me on who should be seeing a psychiatrist and why. The attitude toward psychiatrists, like me, who were doing physical methods of treatment, was not good in those years. After the film was completed, CIBA invited to dinner a large number of psychiatrists and not one showed up. Then people watching the film noted that the patient did not have a grand mal seizure after being given ECT. I got phone calls and nasty letters that I'm a fake, and that I faked this stuff. And I wrote back and said, you have no idea what succinylcholine and amobarbital sodium does. The lobotomy part was very well received. Several neurosurgeons and psychiatrists contacted me with favorable comments.

TB: It's a great film.

FA: Well, I'm not sure whether I did get my message across in the film.

TB: You did several other films as well.

FA: Yes, in 1961, I also did for Merck Sharp and Dohme a film called, *Recognizing the Depressed Patient*, in which I interviewed a number of my patients.

TB: *Recognizing the Depressed Patient* was also published.

FA: Yes, and it sold a hundred and fifty thousand copies. It was a best seller.

TB: Was it translated into any other language?

FA: It was translated by Jean Delay into French. There was also a German translation, but I did not see it. And there was a Spanish one, translated by Lopez-Ibor. They're collectors' items today, if you can find them. Anyway, the film, *Recognizing the Depressed Patient*, was shown and won first prize in an International Film Festival on scientific films. And I was very grateful to all those patients who let themselves be interviewed before camera. I, also, had another film, Tom, which has been very successful. It was on "Drug-Induced Extrapyramidal Reactions" that was made available, I think, in 10 languages.

TB: While doing those films you were involved in research.

FA: Oh, yes. I never stopped doing research in those years.

TB: You were involved primarily in clinical investigations and survey research.

FA: Oh, yes. Well, I did a survey on Drug-Induced Extrapramidal Reactions. It included 33,775 patients. It wasn't a one week or a one month survey. Those people were surveyed over a period of years. And, I'm proud of the fact, Tom, that I published the findings of that survey in JAMA, so that my colleagues, who are not psychiatrists, could be informed about what we psychiatrists are doing, and that we psychiatrists are physicians.

TB: Well, you were one of the few who tried to communicate at the time that we psychiatrists are physicians.

FA: Oh, yes.

TB: Was not your paper in JAMA one of the most frequently cited papers?

FA: Yes, that's correct. On the 100th anniversary of JAMA, they did an analysis finding out the 150 most frequently cited papers of the journal, and my paper was number 20 on the list. It was also the only paper on the list that was written by a psychiatrist. It got a tremendous reception, and a recent survey showed that's still a very, very frequently referred to article.

TB: And then, in the mid-1960s, you started your International Drug Therapy Newsletter.

FA: The International Drug Therapy Newsletter was started after a very strenuous tour of the Orient, Australia, New Zealand, Fiji, Japan, Hong Kong, and Singapore. It was a very strenuous tour. I think it was a British epileptologist, who arranged it, a very well-known one, but I cannot recall his name now. But, at any rate, we met in Tokyo. My first stop was in San Francisco. I did something at the medical school there, and then, went over to Honolulu and did two stops there at the Army hospital and at the medical school. Then, from there, I went to Guam and met with some neurologists there. From Guam, I went to Tokyo, from Tokyo to Singapore, from Singapore to Perth, Australia, from Perth to Melbourne, from Melbourne to Brisbane, from Brisbane to Sidney, and from Sidney to New Zealand. I made several stops in New Zealand. It was summertime there but it was snowing at the top of the mountain.

TB: Was it Mount Cook where you went?

FA: That was the sightseeing place. I stopped there. It was beautiful.

TB: You were in Auckland, also, I suppose.

FA: I was in Auckland.

TB: In Christchurch?

FA: Christchurch.

TB: And, Dunedin?

FA: Yes. I covered all of Australia and New Zealand. Anyhow, in Melbourne, John Cade was my host; and John is, or was, a very devout Catholic. He's dead now, as you know. I hit it off with him, just like that. I learned, from the horse's mouth, so to speak, everything I had ever wanted to know about lithium. We really covered the subject.

TB: So, the International Drug Therapy Newsletter was born after that trip.

FA: It was born after that, yes. As I said it before it was a very strenuous trip and my colleague, the epileptologist, was older than I was. We were not long enough in any one place to really adjust, so he decided to stay and rest in Melbourne. In fact, I think he may have even gone in the hospital for a couple of days, just to be checked. And, I had a marvelous time just going around in those glass bottomed boats and seeing all those beautiful corals and fishes. But you can't do that all day long. So, one night I woke up and began thinking about what I'm doing here. So I had the typewriter that John Cade loaned me. It was a portable typewriter. So, I wrote a little thing to myself. I wasn't in a hypomanic state or drinking. I'm gifted with energy and I have a way of organizing things. I sent the piece to John. He wrote back and thought it was pretty good. So, with that encouragement, I decided to embark on what was to become The International Drug Therapy Newsletter. It was very interesting, the reaction to it. Gerry Klerman, with whom I had been good-friends for many years, wrote me a letter, which I saved, saying, "Frank, I've read the first issue of this International Drug Therapy Newsletter of yours. It's good, but, I'm not going to subscribe to it, because it's going to be out of business in a short time. You'll run out of ideas." So, I said, "OK." So, to make a long story short, twenty-five years later, I sent Gerry a lifetime subscription free. It's still in business.

TB: It's still in business?

FA: Oh, yes. Lippincott Williams and Wilkins bought it from me. If you're getting older you have to be careful with your time. It was a lot of work to keep all those records of subscribers who paid and hasn't paid straight. It is lots of work.

TB: And you wrote the Newsletter without any help.

FA: I wrote the whole thing.

TB: You wrote the whole thing.

FA: Occasionally, a colleague would come to my rescue if I got sick and couldn't get an issue done, so I would, occasionally, invite somebody, whom I thought could do much better than me, on one or another topic. I asked Bob Post or Fred Goodwin or Leo Hollister, and so forth.

TB: Was it distributed worldwide?

FA: Yes, but primarily in the United States. But I had subscribers from Canada, UK, Switzerland, Australia, and New Zealand.

TB: So, it was distributed all around the world.

FA: Yes, but things were getting increasingly difficult because drug companies started to send out reports on their meetings, and others have started their own little things. When I started the newsletter it was the only newsletter.

TB: Yes.

FA: And then, Drug Alert was put out by John Powers and some other publications.

TB: You gathered in the Newsletter all the important events in neuropsychopharmacology monthly.

FA: I tried to.

TB: And you reviewed the material you gathered critically.

FA: Well, there's also another thing I do, Tom, and I've been doing it for some years. I write for *Psychiatric Times*.

TB: Yes.

FA: I write an annual report on the highlights of the APA meeting.

TB: Your writings have an important impact on the field.

FA: I hope it has. I hope it has.

TB: After launching the Newsletter, you organized a very important meeting dedicated to the history of the field.

FA: The Discoveries of Biological Psychiatry.

TB: The Discoveries of Biological Psychiatry.

FA: And, Donald Klein at this meeting, so kindly referred to it at the end of his presentation yesterday, saying, "I couldn't have done this without Frank Ayd's support."

TB: Yes.

FA: But, my idea, Tom, was, “Why not get the guys who have made these discoveries, while they’re still alive, together in one place to tell their story themselves.” And, I proposed this to Dr. Taylor, because the hospital would have to be sponsor for it. I knew that it wasn’t going to be an inexpensive venture, to say the least, because we had to bring in John Cade came from Australia, Lopez-Ibor from Madrid. We had...

TB: You had Pierre Deniker from France.

FA: We had Hugo Bain from CIBA. We had Albert Hofmann, the LSD man from Switzerland. And then, I had my professor in pharmacology, John Krantz, who’s a great lecturer, tell the story of Indoklon, which was never a great replacement for ECT, but still gave hope that there could be some alternatives.

TB: You, also, had the amphetamine story told.

FA: Yes, the amphetamine story told by, what’s his name, the fellow from California. I can see his face in front of me...

TB: Chauncey Leake. You, also, had Tracy Putnam there. He gave the diphenylhydantoin story. What happened to him?

FA: He’s still alive, but I understand he’s quite feeble now. I would think he would be, because, after all, that’s forty years ago, almost, now. No, that’s thirty-one years ago, thirty-two. Well, I was anticipating the possibility that anticonvulsants will end up being mood stabilizers. Tom, I remember this guy, Dreyfus, the big investor guy, who claimed that he was cured of his instability by taking Dilantin. And, this got a lot of publicity. He felt that he had found something that could help a lot of people like himself. And, he assembled, in Florida, some of the top people in business. And in the middle of that meeting, when everybody was just relaxing, television announced that the son of one of the participants, an internist from the Mayo Clinic, had just won the Nobel Prize. And, I’m telling you everyone felt like it was his son. It was quite a celebration. Out of that meeting came a full day symposium on Dilantin at the ACNP meeting in San Juan. Dreyfus came and told his story. He also drew up grant money for various studies done at Hopkins, at Columbia, and so forth, most of which did not hold out much promise for the drug.

TB: Going back to the meeting on Discoveries in Biological Psychiatry, you had Frank Berger there.

FA: Yes, Frank told us his meprobamate story.

TB: Then you also had Joel Elkes.

FA: Joel Elkes, yes.

TB: He had the first department of experimental psychiatry and had done the first double-blind cross-over study with chlorpromazine.

FA: Yes, the first double blind study with chlorpromazine. But, you see, I had to know all those people. I had to know, not only what they did, but who they are, what kind of speakers they are.

TB: You also had Paul Janssen there.

FA: He did the haloperidol story.

TB: The butyrophenone story.

FA: Oh, yes, that's right.

TB: It was in 1970, right?

FA: Yes.

TB: And, you published a book on it with Barry Blackwell.

FA: Yes, Barry and I edited the book.

TB: It was probably also a best seller.

FA: Oh, yes. It's out of print now, but I have the copyright to it and I'm planning to reprint it, sometime, when I find the time.

TB: I am using it very extensively. It is an excellent source book.

FA: That's right. It's very authentic.

TB: Yes, when people tell their own story.

FA: When I wrote to these very well-known guys, I told them if they want to be on the program, they must arrive couple a of days ahead with their manuscript.

TB: To be able to publish the book promptly?

FA: The book was published two weeks after the meeting was over. Barry would edit the chapters as we got it from them. When they presented their papers, they already had the edited version in hand. And on Sunday night, after the meeting was over, I sat up with a guy from Lippincott till about three in the morning, finishing off the final touches. It was a lot of work.

TB: In the early 1970s you became involved in drug delivery systems.

FA: Absolutely.

TB: You recognized the importance of giving neuroleptics in long-acting depot preparations. Would you like to talk about that?

FA: Well, if a drug is going to be beneficial to someone, the person will have to take it by a particular route, and you might enhance the benefit by by-passing some metabolic pathways, if given parenterally instead of orally or by a deep intramuscular injection instead of subcutaneously. Actually, the story of depot preparations is an interesting one, Tom. I did the first study on fluphenazine for Schering and the company was doing quite well with the success of the drug. This might have been the reason that Charlie Revlon was buying up Schering stocks. Schering wanted to stop this, and the only way they could do it was to merge with another company. So they merged with White Laboratories. I knew White Laboratories very well, because they were predominately a pediatric pharmaceutical company, and my father had contacts with them. They produced a lot of vitamin preparations for children. It turned out that those vitamin preparations came from Squibb. So, anyhow, to get Revlon out of the picture, the merger between Schering and White Laboratories was finalized. The agreement was that Schering would continue with fluphenazine at an adult dose, whereas White, being known as a pediatric pharmaceutical company, would market a low dose of it. Well, shortly thereafter, Squibb, which had already developed a way of producing a depot formulation, said to White Laboratories, we want the rights to fluphenazine, and if we don't get it, we will not produce the other stuff for you any more. Basically, that's what it was. So, that happened. So, then, they developed a depot formulation of the drug. The first one was the enanthate that worked for two weeks. And then, with some more structural manipulation, they got the decanoate that lasts from four to six weeks. That was the beginning of the depot formulations. Now, there are close to twenty-seven or twenty-eight different depot preparations of antipsychotic drugs available, and you're going to see some of the atypical depot preparations in the not too distant future.

TB: The availability of drugs in depot preparations is very important for developing countries, like India. They use them, probably even more extensively than we use them in the Western World.

FA: Oh yes. But depot preparations also have their drawbacks. There are inconveniences associated with them. I mean, either a nurse has to go to the patient or the patient has to come to a clinic. So, the clinic has to operate on schedules that people can come, say at night, because they can't get off from work without losing their job, to get their shots, usually. So, a lot of things are

involved in it. I envision that eventually we will see olanzapine, risperidone, ziprasidone available in depot preparations. Clozapine, I think, would not be available because it would be too risky.

TB: You were also director of research and education at the Taylor Manor, and professor at...

FA: West Virginia; University of West Virginia. Tom, to be perfectly truthful, that was never intended. The young fellow, I had known for some time, who became chairman there had an accreditation visit shortly after he took the job. And, there he was, a young man, about thirty-five with all the residents without senior people, so to speak. So, the question was raised, where are your old people? I don't have any, he said. He was asked why he is not getting some senior people in to help out. So, he called me and asked me if I would come down and help him. So, I went down, and the agreement was that I would teach a certain number of hours every month. Usually I went down either Wednesday and be there Thursday and Friday and came back Saturday morning, or go down on Sunday evening and be there Monday and Tuesday and come back Wednesday. That worked fine and I was pleased. They were pleased. I'm still, officially, on the faculty and still get invited to graduations and all the faculty ceremonies, but in fact I haven't been there to teach for the last few years.

TB: You became emeritus at Taylor Manor, in 1987, I think, and when you became emeritus they changed the name of the library of the hospital to...

FA: Oh, yes. You know, I'd been admitting patients to that hospital since 1951. I built that hospital's reputation, even before I became the director of professional education and research. And, to show their appreciation Dr. Taylor said to me, "I'd like to name the library the Ayd Professional Library at the hospital." They had a little ceremony and put a plaque on the wall. So, a number of doctors from Washington came and we had a very pleasant luncheon. It was nice. I felt very glad about whatever I'd done to help them and their patients.

TB: ACNP also recognized your contributions. You were recipient of the Paul Hoch Award.

FA: The College has given me two awards.

TB: The other one was the Distinguished Service Award.

FA: That's right. That's correct.

TB: But, the same year when you got the Paul Hoch, you got also another distinction, The Open Mind Award.

FA: Yes, from the Janssen Research Foundation. That year, it was Pierre Deniker and myself who got that award. Since then, Hans Hippus, and the fellow who was in New York and now is back to Holland...

TB: Herman van Praag.

FA: Yes, Herman van Praag, he also got it. I don't know if it has been given since that time to anyone else.

TB: Then, *The Psychiatric Times* gave you also an award.

FA: Yes, yes, they did. They gave me The Lifetime Achievement Award.

TB: You got it in the early nineties.

FA: Yes, and they gave Paul Janssen the same award also that year, and to somebody else, as well, but I've forgotten who it was.

TB: In the mid 1990's, you were listed among The Best Doctors in America.

FA: Yes. I don't know how that happened. I think they wanted me to buy a copy of their book. Still, it's an honor somebody thought I deserved to be listed.

TB: Then, in the mid-1990s, you also got The Distinguished Professor Award from The Center of Psychiatry.

FA: That's right. Tom, I've been blessed. There's no question about that; I've been blessed. As a Catholic, for example, I was honored to become a member of The Holy Name Society, and to my knowledge, I'm the only psychiatrist that The Maryland Holy Name Society awarded this honor. And then, I got from the Palatine Fathers, the Saint Vincent Palatine Award for service to the church and the state. These things always come as a surprise to me.

TB: They were well deserved.

FA: Well, you know, when it happens, you're grateful that it happened. But I have a duty to teach my children don't let pride become a big item.

TB: Now, all through those years, you did practice and saw patients.

FA: That's right.

TB: And, you said that, at the beginning, you had your practice in your father's office.

FA: Oh, yes, that was only for about a year.

TB: And, then, you moved into...

FA: I moved into a wing of my home. I bought an old country home, tore down the barn, and got them to dig out the foundation, run in the water and all that sort of stuff. Then I moved immediately full time into the office. And, the office was set up in such a way that there were two floors. In the basement we had beds where I could give ECT. And then, on the other side of the basement, there were four offices for interviewing patients that the psychologists and social workers could use. On the first floor, there was a big reception room, my office, offices for two psychologists, or internists, or whoever was working at the time with me. And then we had storage place for the records of the patients.

TB: Did you have usually two psychologists working with you?

FA: Yes.

TB: Did you also have psychiatrists working with you?

FA: Yes.

TB: How many?

FA: Well, it varied. It really varied. I had a very fine board certified psychiatrist from Argentina who was very fluent in English. He was a distinguished looking and soft-spoken man. He worked for me until he died. He died, prematurely of cardiac arrest. And, then I had a fellow, whom I'd met in a strange way. You know, I'm a Catholic and I have never charged widows and so forth. And, God has been good to me, so I pay Him back any way I can. I used to go to the Bahamas, once a year, and donate a month of my time to the church and outpatient clinics there. And, I also help in the psychiatric hospital. These things were my way of saying, "thank you." I've lost my train of thought. What was the question before?

TB: We talked about your office, about people who worked for you, and that one of the psychiatrist working with you that you met while donating your time to the Church in the Bahamas.

FA: He was a board certified psychiatrist who was also donating his time to the Church. He was down there with this wife and two children, and he wanted to go into private practice. So I gave him a job. His wife was expecting their third child, then. So, we gave them the third floor of our house to live up there. He would be on call twenty-four hours a day.

TB: So, you usually had at least one psychiatrist to cover for you when you were away, right?

FA: No, actually when I was away, Taylor Manor Hospital covered for me.

TB: Oh.

FA: They had people on duty twenty-four hours a day. I have almost forgotten but I also had a fellow working with me, who ultimately became a neurologist. During his residency, he got married and his wife was expecting a child. So he needed some extra income. He did physical exams in the office.

TB: And all through the years, you have been doing clinical investigations in your practice.

FA: Lately, I've been involved more, as a consultant, than in actual research. You get to the point in this business, so to speak, Tom, that you begin to put together which way the wind is going to blow with one or another particular compound. For example, I had a tremendous experience with the depot neuroleptics, so Squibb had me go to the Orient, and I gave lectures in Singapore, Hong Kong, and Tokyo. They, also, had me in Australia to give some seminars on depot neuroleptics, setting up the clinics, and that sort of things. It is important how you set up the clinic, how you schedule the appointments, and how you consider the patients. Doctors can be cruel people, Tom, and I've witnessed this in clinics, you know, where patient comes in to get a depot injection, and some guy pulls the dress up and pulls the pants down, while the patient is menstruating. You know, it's a terrible thing to do. And that creates hostility on the part of the patient, and boy, you try to get them back – it's impossible. Now, for example, recently at a meeting of one of the pharmaceutical companies that has an atypical neuroleptic to be studied in a depot form, I listened to their plans and said, "You're going down the wrong road. This isn't going to work"; and I pointed out that you need to schedule things properly and for this you've got to have nurses who understand this; you've got to train people; it's not just a matter of injection; you've got to know how to use the needle so that it wouldn't hurt. These are very simple things that apply to all of the depot neuroleptics.

TB: So, lately you have been more involved in research as a consultant. Which were the last drugs you were actively involved with as a clinical investigator?

FA: I worked with zimelidine. That was an unfortunate story. It was a very good antidepressant drug, and then, "bingo," something that you could not predict from animal data happened. Before it was released for clinical use, Tom, they brought together a remarkable board of experts to advise them. Leo Hollister, Bob Post, Malcolm Lader, I, and many others were there. The company wanted to be a success without any risk to the patients, whatsoever. They had had a couple of

other drugs that had backfired on them, so they were really touchy about this thing. And, they brought us all to Sweden and treated us very graciously. There were no holds barred on the data. We saw all of their data, and it was the consensus that it was a good drug, and as you know, it was marketed, but unfortunately it produced neurotoxic effects.

TB: So it was zimelidine the last antidepressant you were involved with as an investigator. What about antipsychotics? Which was the last antipsychotic you were directly involved with as an investigator?

FA: Well, the last one would have been clozapine.

TB: Clozapine.

FA: I got involved with clozapine in a strange way. Warner Company in Bern, Switzerland, a small pharmaceutical company, invited me over to give a talk on antidepressant drugs. I wondered why, because they didn't have any antidepressant, to my knowledge. And, I went over, and after I gave my lecture, they showed me data they had on a new compound that they thought to be an antidepressant drug, and they wanted me to do a study with it. So, I brought back with me the data, and after studying what I got, carefully I wrote them back and said, I'd be willing to do a study. And the drug turned out, Tom, to be a very effective antidepressant in a certain dose-range. I had seen no serious adverse effects with it until ninety percent through the study. It looked very good, then "bingo," a fatal agranulocytosis occurred in an elderly woman. And, of course, I reported it to Warner. The drug turned out to be a predecessor of clozapine. So, shortly after that, they merged with Sandoz, and Sandoz got all the derivatives of this compound. And, I ended up being consulted by Sandoz, quite frequently. I'd fly over to Basel, Switzerland for a weekend, or for three or four days. This is how I got involved in a small study with clozapine.

TB: From early on, you were frequently one of the first to describe one or another adverse effect of a new drug. Didn't you write something about akathisia and suicide recently? Were you the one who thought first that there was a possible relationship?

FA: No, I was not. I was the first to say that people who say that are wrong. What happened, Tom, was that there were a number of letters to the editor on akathisia and suicide based on very weak scientific data. I wrote a rebuttal to some of these letters that was published. Just recently, I published an issue of the Newsletter on extrapyramidal reactions with the various atypical antipsychotics, and the fellow, who wrote it for the Newsletter, brought up the issue of potential

suicide because of akathisia. I wrote a rebuttal to that and it's been published. If you'd like to see it, I'll send you a copy.

TB: I knew you wrote on the topic and I should have read it.

FA: Well, the difficulty is that both akathisia and suicidal ideation are common and statistically you are going to have X number of persons who have suicidal ideation and akathisia together.

TB: So, you don't think that there is a relationship between them.

FA: There isn't. There isn't any. Now, it's possible that akathisia make some people so uncomfortable that they act impulsively, but this is not necessarily a suicidal action induced by a desire to die.

TB: In the middle of the 1990's, you became involved in writing a book in collaboration with some people...

FA: John Davis, Sheldon Preskorn, Phillip Janicak and myself, yes.

TB: It was on "The Principles of Psychopharmacology."

FA: *The Principles and Practice of Psychopharmacotherapy*. The third edition just came out. It's been very successful. The second edition is now translated into Russian, and now, there are negotiations to have it come out in Chinese and Japanese. It's been a very successful book. It's very practical and fairly comprehensive. If you pick up a copy of the latest edition, the foreword to it was written by Jonathan Cole and Jonathan was very laudatory in his comments on the structure of the book, its coverage in terms of comprehensiveness, and its clarity of presentation. It's a good book for practitioners. Whether we'll have a fourth edition, who knows?

TB: It seems to be very successful. And the same applies to your Lexicon that is also very successful.

FA: The first edition of the Lexicon was quite successful. The sales of the second edition have been a delight. And, the reviews of it have been, I think, very objective and laudatory.

TB: The Lexicon covers psychiatry, neurology and neuroscience. It is really more than a Lexicon. It's like an encyclopedia.

FA: Well, Floyd Bloom was a peer reviewer of it. He's a very busy man, editor of Science, and he was the first to comment that, "This is no longer a Lexicon. This is an Encyclopedia." And, I took a poll of other people whose opinion I respect, and there were many of them who agreed with him. There were a few dissenters, who felt that in the minds of people this was established as a

Lexicon, and if we try to change it to Encyclopedia, it'll confuse people and they will not be inclined to buy the third edition, and five years of labor will be going down the drain.

TB: You had an editorial board. But, it seems to be that you did most of the work.

FA: Editorial boards have perspectives but if you respect the people on the editorial board enough to have them on the board, you ought to respect their judgments, unless it's so way off beam. And, I picked some psychiatrists because of their broad experience and some very bright, young psychiatrists. I didn't expect them all to be expert writers. They could write some things or call my attention to something, and they were very helpful. I'm grateful to them; I tell you that. But, basically, the writing is mine.

TB: How long did it take you to write it?

FA: Five years. The second edition took five years. It has a thousand new entries in it, and the size of the book increased from 500 to 1200 pages.

TB: One of the reviewers of the book said in his review that no one else could have done this, and it's true.

FA: Well, I'm glad to hear you say it's right.

TB: Could you mention some of the people who might have had an impact on your professional development?

FA: Tom, there are very many that I could name, but will pick out for you just a few. One of them was Paul Janssen. He is clearly a great pharmacologist. Paul Janssen is not a psychiatrist, but he's a genius. He's got a gift. Paul and I met under strange circumstances, at an annual meeting of The American Academy of Chemistry, in New York. He was presenting a paper on "How To Cure It All" and I presented a paper on "Structure Activity Relationships." I didn't meet Paul before but I knew who he was, by reputation. And, after he delivered his paper, I went over and talked to him; we ended going out to dinner; and that was the beginning of a very valuable friendship, for me anyway, and I hope for Paul also. I've spent many hours with Paul at his home and at meetings. Another person I would like to mention is, of course, Heinz Lehmann. Then Malcolm Lader is also one.

TB: Just one more question. Do you think your expectations at the beginning of your career to bring back psychiatry into medicine are fulfilled?

FA: We're not a hundred percent there, but we're getting there. I mean, there's no question about it. Look at what Representative Kennedy had to say yesterday about the attitude of people toward a person who has a physical illness vs. the attitude of the public toward a person who has a psychiatric illness. The stigma is still there. There's no question about that and we've got to eliminate that. We're getting closer to it all the time. We've got to educate the public. That's one of the reasons, in fact, why I did that television show on ABC many years ago. I didn't get paid for that. I had a lot of headaches because of it; because I was trying to run a practice and they were running wires through my house.

TB: Do you think we are moving in the right direction?

FA: Yes, we are moving in the right direction.

TB: Is there anything else you think that should be mentioned?

FA: No. I think we have a right to be proud.

TB: I think we are proud, lucky and thankful to you that you were willing to share all this information with us. Thank you very much.

FA: You're more than welcome.

2. HERBERT BARRY III

TB: We are at the 48th annual meeting of the American College of Neuropsychopharmacology in Acapulco, Mexico. It is December 12, 1999. I will be interviewing Dr. Herbert Barry III.⁴ I am Thomas Ban. Let's start from the very beginning. Could you tell us where you are from and something about your education and early interests?

HB: I'm Herbert Barry III, Tom. I trust that for you, I'm Herb rather than Herbert Barry III. I have been told that my parents both grew up in the New York area and that I was born in Doctor's Hospital in New York. They moved to Cambridge, Massachusetts before I was born. My maternal grandparents wanted me to be born in New York City. I grew up in Cambridge, Massachusetts for the first sixteen years, when my family moved to Brookline, Massachusetts. I went to college, undergraduate, at Harvard in Cambridge, Massachusetts. My father, all three uncles, and one of my grandfathers also had graduated from there, so it was a family tradition. I went to graduate school in psychology at Yale, where I got my PhD. degree in 1957. I continued at Yale as a post-doctoral research fellow and then as a junior faculty member, doing full time research, sponsored by Professor Neal E. Miller. My first job elsewhere, in 1961, was at the University of Connecticut in Storrs. In 1963, I moved to the University of Pittsburgh, Department of Pharmacology School of Pharmacy. This was my first residence outside of New England. I have been in Pittsburgh ever since at the School of Pharmacy.

TB: How did you decide to enter psychology and get involved in psychopharmacology? HB: It was quite an individual influence. My major in graduate school was experimental psychology, and essentially, it was what we called "rat running," using laboratory rats as models to test learning, memory, and behavior, as applicable to humans. My PhD dissertation was entitled, "Effects of Strength of Drive on Learning and on Extinction."

TB: So your Ph.D. was in experimental psychology.

HB: My dissertation tested a rather simple situation. The rats ran down a straight alley to get a food pellet. I measured the duration it took them, to the nearest hundredth of a second. When I was

⁴ Herbert Barry III was born in New York, New York, in 1930. After undergraduate studies at Harvard University, he completed his Ph.D. and post-doctoral studies in experimental psychology at Yale University. Throughout his academic career he was on faculty at University of Pittsburgh in the Department of Pharmacology in the School of Pharmacy. He was interviewed in Acapulco, Mexico on December 12, 1999.

finishing my PhD degree, my psychoanalysis, which began in my first year in graduate school, was still continuing, so I had an incentive to stay in New Haven for a while longer to finish the psychoanalysis. I wanted to apply for a post-doctoral research fellowship. I almost applied for a fellowship from the National Institute of Mental Health, NIMH, to be sponsored by Irvin L. Child, a developmental psychologist, to extend some of the research I had already been doing with him on child training practices in a world sample of societies.

TB: Are we in the 1950s?

HB: Yes, it was in 1957. Neal Miller, who was the major advisor for my PhD dissertation, had started doing psychobiology research. He said that psychopharmacology was a new and rapidly developing field. In 1957, it certainly was. He suggested that I apply for a post-doctoral research fellowship from NIMH in psychopharmacology. He felt that there would be a better chance of it being awarded and funded in that area. And I was fascinated by the topic of drugs.

TB: You have been working with a conditioning paradigm?

HB: It was instrumental rather than classical conditioning, but it was a conditioned behavior.

One of the hypotheses tested in my Ph.D. thesis was that a change in the rat's motivation, from a longer to a shorter deprivation of food, or from a shorter to a longer deprivation of food, would affect its running speed because of the change from the previous experience of running to the food pellet under the other degree of food deprivation. In my post-doctoral research fellowship with Neal Miller, I did a behavioral analysis of drug effects. We constructed an alley in which the rats had an approach-avoidance conflict and then we tested the effects of drugs on the rats' performance. We found that alcohol and amobarbital would decrease the avoidance more than it decreased the approach component of the conflict. The rat was intimidated by shock when it approached the food cup and got a painful electric shock at the cup. The rat therefore avoided the cup. Under the influence of the drug it became bolder or less deterred by the shock. That was the beginning of my psychopharmacology research.

TB: So, you found that alcohol and barbiturates decreased the avoidance component more than the approach component?

HB: Yes, and we also tested several other drugs. Chlorpromazine was one. We did a little bit of work with morphine.

TB: And, all these drugs decreased the avoidance component with little effect on the approach component?

HB: Yes. I was a post-doctoral research fellow for two years. During that time, Neal Miller applied for a research grant in psychopharmacology with me as his co-investigator, not coprincipal investigator. I became an instructor, and soon afterward, an assistant professor at Yale, during the two more years I stayed with him on that project. It was quite successful. We published articles in *Psychopharmacologia* and in the *Journal of Comparative and Physiological Psychology*.

TB: What was your first publication?

HB: It was Neal E. Miller and Herbert Barry III, "Motivational Effects of Drugs: Methods Which Illustrate Some General Problems in Psychopharmacology." It was published in Volume 1 of *Psychopharmacologia*. Its citations included a couple of articles from 1935 and 1936 by Neal E. Miller and Walter R. Miles, which reported psychopharmacology experiments on rats.

TB: In what year was your paper published?

HB: In 1960. The manuscript was received by the Journal in October 1959. We subsequently published several other studies together. In 1961, I accepted a job as assistant professor of psychology at the University of Connecticut, where I continued research in psychopharmacology. In fact, I was principal investigator of a research grant that I applied for at the University of Connecticut.

TB: What was that grant for?

HB: It was on stress. The title was "Situation-Drug Interaction in Emotional Responses."

TB: How did you induce stress?

HB: One of the ways was by exposing the animals to severe painful shock prior to injecting the drug. Also, I was continuing some studies on approach-avoidance conflict.

TB: You were probably among the first to do this kind of research in North America.

HB: Yes, Hannah Steinberg did some similar studies in England. Neal Miller had been the major advisor of John J. Conger, who did a Ph.D. thesis on alcohol. I was one of the early Americans to do laboratory animal research in psychopharmacology. I was offered a job at the University of Pittsburgh, in 1962, during my second year at the University of Connecticut. The research project there was well funded by NIMH. The principal investigators, William J. Kinnard and Joseph P. Buckley, were professors in the Department of Pharmacology, University of Pittsburgh School of

Pharmacy. They had been awarded a grant and Oakley S. Ray was expected to do the behavioral research on it. The title of the project was "Analysis of Psychopharmacologic Methodology." Since the emphasis was on behavior, a psychologist was needed for the project. Kinnard and Buckley were both pharmacologists. Oakley Ray was listed as the principal investigator when the grant was awarded. After a dispute with Joe Buckley, the Chairman of the Pharmacology department, Oakley Ray decided to withdraw from this project. He had a job at a Veterans Administration Hospital in Pittsburgh. After the five-year grant had begun, Buckley and Kinnard were looking for a psychologist to run the experiments and direct a large part of the research. They recruited me. Neal Miller had been a member of the committee that established and approved this project. I met Buckley and Kinnard, and the project seemed like a very good opportunity to focus on my research; I had considerable teaching duties and rather meager laboratory facilities at the University of Connecticut in Storrs. That university now has a medical school in Farmington with great facilities.

Although Neal Miller advised me against accepting the job, I accepted it, and started in February 1963, at the University of Pittsburgh, as a research associate professor of pharmacology. I was well aware it was funded by a research grant that might expire in four years. I expected it would be a temporary job, but I'm still there. It is ironic that when I accepted the job at the University of Connecticut, I expected it would be my long-term future career.

TB: So, you have been for many years in Pittsburgh by now.

HB: Yes.

TB: What was your role in the project?

HB: Bill Kinnard was the principal investigator and Joe Buckley, the Chairman of the department, was the person who really directed the project. I conducted the portion of the project that involved operant conditioning. We focused on trying to establish the optimal techniques for testing effects of chlorpromazine. My part of the research was on conditioned avoidance response. Chlorpromazine, as you well know, suppresses avoidance response. It does not interfere much, if at all, with the animal's ability to escape the shock. The animal waits until the shock begins before it presses the lever or makes whatever other response to terminate the shock.

Avoidance performance is very much impaired.

TB: Weren't some other people also doing somewhat similar research at that time?

HB: Leonard Cook was doing research on conditioned avoidance in squirrel monkeys. I also know of an article by Geller and Seifter, published in Volume 1 of *Psychopharmacologia*.

TB: Did you do your experiments in rats?

HB: I did it in rats, yes, as did Geller and Seifter. George A. Heise also was doing research on conditioned avoidance in rats. I don't think he used chlorpromazine. He was one of the original investigators of the benzodiazepines.

TB: Were you the first to establish in rats that chlorpromazine suppresses the avoidance response without having an effect on the escape response?

HB: Oh, no. My research on the conditioned avoidance response used two levers. The animal pressed one lever to avoid the shock and a different lever to escape the shock. That technique was described by Heise and Boff, in 1962, in an article entitled, "Continuous Avoidance as a Baseline for Measuring Behavioral Effects of Drugs," published in Volume 3 of *Psychopharmacologia*. Prior to the publication of that article, Murray Sidman had developed the technique for conditioned avoidance. For two or three years, at the University of Pittsburgh, I concentrated on that technique and also cooperated with colleagues on the project. One of these colleagues, Nathan Watzman, was assigned to do research on the effects of drugs on motor activity in mice. For a couple of years I worked closely with him, particularly on writing and publishing the findings of those studies.

TB: Did you study the effect of drugs on spontaneous motor activity?

HB: Yes, on spontaneous motor activity in a circular arena. We published several articles on it together in the *Journal of Pharmaceutical Sciences*. In 1966, the sponsors of the research project on which I was employed expressed dissatisfaction with the research. Their criticisms applied less to my part of the research than to other parts. We were advised not to apply for continuation of the prior program project. We were told that if we wanted to continue doing the same research, we ought to apply for it in a grant with a new name. The members of the review committee for that program project had changed, and the new members did not like the kind of research we were doing. That project therefore was terminated.

TB: What did you do after the project was terminated?

HB: I then applied for a research grant. And Joe Buckley also encouraged me to apply for a research scientist development award from NIMH at the same time. Both of them were approved and funded shortly before termination of the research grant on which I was employed. A few years

later, in 1970, I was promoted from research associate professor, outside the tenure stream, to tenured professor in the department. In 1970, the same year, the Elsevier Company published a book on *Actions of Alcohol* that I co-authored with Henrik Wallgren. Our purpose was to summarize scientific knowledge about ethyl alcohol. I believe that book contributed to my promotion. Henrik Wallgren is a very distinguished physiologist in Finland. The Elsevier Publishing Company invited him to write a book summarizing scientific knowledge about alcohol. He was asked to do it with a psychologist, preferably an American. Neal Miller recommended me to him. Wallgren wrote the invitation to me in 1963. I visited him in Helsinki, in 1964, and we worked well together. It took us six years to finish this book, which consisted of two volumes. The original tentative title of our book was *Actions of Ethanol*. My father, Herbert Barry, Jr., asked me sarcastically if we used the word "ethanol" instead of "alcohol" for the purpose of minimizing the number of readers of our book. He was trained as a psychologist and then he became a psychiatrist. He and I published several articles together in the 1960s, on psychiatric implications of season of birth and on birth order in the family.

TB: You published articles on the effects of alcohol with Neal Miller. Didn't you publish also some other papers on the effects of alcohol on your own?

HB: My articles with Neal Miller were on effects of alcohol on approach-avoidance conflict in rats. My earlier publications included a paper, in 1968, on socio-cultural aspects of alcohol addiction, and another paper, in 1969, with my father and Howard T. Blane on birth order of delinquent boys with alcohol involvement. All these papers were cited in my book with Wallgren. Our book included findings on the physiological, neurological, and behavioral effects of different types of alcoholic beverages. We divided the work on the book so that Henrik Wallgren wrote the initial draft of half of the chapters and I wrote the initial draft of the other half. He wrote the chapters on the physiological and neurological effects of alcohol, on alcohol metabolism, and on interactions of alcohol with other drugs. I wrote the chapters on voluntary consumption of alcohol and on behavioral studies on laboratory animals. I also wrote a chapter on alcoholism, which was the first of my series of papers on alcoholism. It dealt with personality characteristics that make a person either vulnerable or resistant to develop alcoholism.

TB: So, you were involved in studying the effects of alcohol quite intensively?

HB: Yes, I had done some initial studies on alcohol with Neal Miller, at Yale, and then I did some more at the University of Pittsburgh. I worked on the book from 1964 until 1970. I published articles on birth order of alcoholics in the 1970's, because as a psychologist, I was very interested in social and developmental factors. This interest was concurrent with my research on laboratory animals in behavioral psychopharmacology.

TB: Could you tell us something about your findings in your birth order study?

HB: Alcoholics are more often last-born from large families of four or more children. That was our principal finding. Howard T. Blane and I summarized results from many studies on alcoholic men in an article on "Birth Order and Alcoholism; a Review," published in 1973, in the *Quarterly Journal of Studies on Alcohol*. Our interpretation of the finding was that the last-born child in a large family is customarily treated as the baby of the family. The mother does not desire to have the youngest child become assertive and independent. This induces a conflict that is especially severe if the youngest child is a boy. A general psychoanalytic theory suggests that many alcoholics are conflicted between being dependent and becoming independent. The children are unwilling to acknowledge their very strong desire to be dependent and taken care of and are also unwilling to act out their dependence. Intoxication is a way to be dependent on alcohol or another drug and, at the same time, to deny one's pharmacological dependence. For example, the person who is drunk will have fantasies that he is very powerful. He may get very pugnacious, saying, "I can beat up anybody else in this bar." This is our explanation of the finding that alcoholics are most often the last-born child in a large family. An alternative possible explanation is that the last-born child is more likely than earlier born children to be hospitalized for alcoholism, not necessarily because of having a more severe drinking problem.

TB: So while you did behavioral research, you maintained your interest in psychodynamics.

Did you finish your training in psychoanalysis?

HB: My psychoanalyst suggested that we finish the analysis soon after the beginning of my post-doctoral research fellowship. He and I agreed that it was the appropriate time. I believe it was a good experience. I am skeptical about some of the Freudian psychoanalytic doctrines, but I have maintained an interest in the topic. I contributed a chapter on "Psychoanalytic Theory of Alcoholism" to a book on *Theories on Alcoholism*, published, in 1988, by the Addiction Research Foundation in Toronto, Canada. The Editors of the book were C. Douglas Chaudron and D. Adrian

Wilkinson. I enjoyed preparing the chapter. An unusual feature of my chapter was that I summarized Sigmund Freud's published writings about alcohol effects and alcoholism.

Ever since I was an undergraduate at college, majoring in Social Relations, I have been very interested in personality dynamics and developmental factors. My first rat experiment, in my first year in graduate school, compared the memory of very young rats with mature rats for previously escaping from an electric shock in a runway. My psychoanalyst pointed out that I was fascinated by the question of how well a very young individual would remember an experience compared to a mature individual. That initial experiment was unsuccessful, but fortunately, my subsequent experiments in graduate school were successful. That is a digression from psychopharmacology.

TB: So let's get back on the track; what were you doing in Pittsburgh?

HB: Several years before Henrik Wallgren and I finished the book on alcohol, I started doing research on the discriminative stimulus attributes of drug effects in laboratory rats. It is sometimes called drug discrimination. The human experimenter trains the laboratory rat to inform the experimenter whether it feels drugged or normal. A hungry rat is trained to press either of two levers to obtain a food pellet in a chamber that contains a food cup. After this preliminary training, one lever delivers food only if the rat has been injected with placebo and the other lever delivers food only if the rat has been injected with a drug. An equal number of sessions are preceded by placebo and by the drug. The interval between successive sessions is two or more days to permit complete recovery from the effect of the drug or placebo.

The rat gradually learns to press preferentially the lever that delivers food, depending on whether the session was preceded by the drug or placebo. In a training session of ten or fifteen minutes, no food is delivered in the first one or two minutes. We count the number of times the rat presses the two levers during this initial part of the session. After more than twenty, but less than forty sessions, divided between the drug and placebo conditions, the rat in the initial interval without food usually presses more often the lever that will deliver food in its current condition. The rat therefore responds to the internal differential drugged or normal condition.

It is a technique that was initiated by Donald A. Overton. His first article on this technique, "State Dependent or 'Dissociated' Learning Produced with Pentobarbital," was published, in 1962, in the *Journal of Comparative and Physiological Psychology*. A more extensive report, "State-

Dependent Learning Produced by Depressant and Atropine-Like Drugs,” was published, in 1964, in *Psychopharmacologia*. Overton trained and tested rats in a T-shaped maze. Food was at the end of one arm, under the drug condition, and at the end of the opposite arm, under the non-drug condition. My first publication on drug discrimination research also used a T-shaped maze. Alcohol was the drug discriminated from placebo. It was a one-page article I wrote with coauthors Eileen Koepfer and Joyce Lutch, with the title “An Operant Procedure for Training Discrimination between Drug and Nondrug State,” in 1965, in *Psychological Reports*. Koepfer and Lutch were high school students who did the research project under my direction.

Since primacy is an important factor in science, I can claim to have originated drug discrimination research in an operant conditioning box containing two levers. This apparatus has been used frequently in a great variety of studies. A novel technique was to establish drug discrimination in rats that had been trained to alternate the condition of the light in the chamber, on and off, by successive lever presses. Illumination was associated with food after alcohol injection for half the rats and after placebo injection for the other rats. Successful training was reported in my article “Prolonged Measurements of Discrimination between Alcohol and Nondrug States,” in 1968, in the *Journal of Comparative and Physiological Psychology*. In the same area of research, Robert K. Kubena and I published, in 1969, two subsequent articles. “Two Procedures for Training Differential Responses in Alcohol and Non-drug Conditions” appeared in the *Journal of Pharmaceutical Sciences*; “Generalization by Rats of Alcohol and Atropine Stimulus Characteristics to Other Drug” appeared in *Psychopharmacologia*. Both articles are based on the master’s thesis of Kubena. I was his principal advisor in this research and in his subsequent Ph.D. dissertation. I initially felt apprehensive about advising Bob Kubena to undertake a project that required maintenance and training of the animals for several months before obtaining useful data. There was meager prior information on this research technique. Fortunately, he conducted the initial experiment and subsequent ones very proficiently and successfully.

I continued the research on drug discrimination for many years, from 1967 to 1983, with the support of a research grant for “Behavior and Drug Effects during Chronic Stress” from NIMH. The principal use of the drug discrimination technique has been to test other drugs to find out if another drug is more similar to the training drug or to the placebo. Also, tests with different doses of the drugs can determine the minimum effective dose. In the early studies, Don Overton and I

both showed that alcohol and a barbiturate could substitute for each other. Rats trained to discriminate either drug from the placebo make the drug response when tested with a sufficiently high dose of the other drug. A drug discrimination technique that I subsequently used was to train animals to discriminate between two different drugs, such as between alcohol and pentobarbital, instead of between either of the drugs and placebo. Although the discriminative effects of these two drugs are similar, they are not exactly the same. Differential discriminative effects are found in rats trained to discriminate between several doses of alcohol and several doses of pentobarbital.

I relinquished my animal laboratory, in 1995. I am now writing some historical reviews of psychopharmacology.

TB: What are you writing about on the history of psychopharmacology?

HB: My most substantial work in this area was *A History of Division 28*. Division 28 is the division of psychopharmacology and substance abuse of the American Psychological Association. My historical account was published, in 1998, by the American Psychological Association, in volume 2 of a book on *Unification through Division: Histories of the Divisions of the American Psychological Association*. The book was edited by Donald A. Dewsbury. The very large American Psychological Association is organized into more than fifty divisions. Division 28 was founded, in 1966. I was one of the founding members of that division and its president, in 1981. The membership of the division is approximately 1000 people, a small percentage of the total membership of the American Psychological Association, but a sufficiently large number of people to sponsor the division's programs at the annual meetings and to make substantial contributions to psychopharmacology.

TB: How many members are in the American Psychological Association?

HB: More than a hundred thousand, I believe. The American Psychological Association decided to publish several volumes containing histories of its different divisions. The Division of Psychopharmacology recently changed its name to "Division of Psychopharmacology and Substance Abuse." By the name change, it tries to broaden its scope. More recently, I coauthored an article with Donald A. Overton and John A. Rosekrans on the "Creation and First 20 Years of the Society for the Stimulus Properties of Drugs (SSPD)" that was published, in 1999, in *Pharmacology, Biochemistry and Behavior*. I presided over the first meeting of the SSPD, in 1978, and I was, in 1980, the third president of the organization. Several international meetings of that

society were held in Beerse, Belgium, and sponsored by the Janssen Pharmaceutical Laboratories. Francis C. Colpaert did excellent research in those laboratories. The SSPD is a small society, with fewer than two hundred members, but I believe it is an integrative force for its specialty topic.

TB: So, you were one of the founders of that society, and one of its early presidents.

HB: Yes. I was one of the early contributors to that specialty topic.

TB: Could you explain to us what it means when you say, "stimulus properties of drugs."

HB: A drug effect functions as an unconditional stimulus. I remember having been told that Pavlov's term in Russian was mistranslated as "unconditioned stimulus" but should be translated as "unconditional stimulus." The drug effect is an unconditional stimulus in the central nervous system. A stronger, and therefore, more effective unconditional stimulus is the rat's hunger. Food pellets constitute an unconditional stimulus. The unconditional response is eating food to alleviate the unconditional stimulus of hunger. The differential drug and non-drug conditions during the training sessions become distinctive conditional stimuli, associated with the differential conditional responses of pressing the different levers to obtain the unconditional stimulus of a food pellet. If a conditional response is learned under the influence of a drug effect, that conditional response is specific to the drug effect and to the function of the nervous system under the influence of the drug.

TB: So the unconditional drug effect becomes a conditional stimulus?

HB: Yes. Therefore, an individual animal or human can be trained to make differential responses and acquire different habits. One habit is acquired under the influence of the drug conditional stimulus. A different habit is acquired under the influence of the normal or non-drug conditional stimulus. It is like training the rat to distinguish whether it is drugged or normal. Pharmaceutical companies used this technique a great deal in recent years. Animals are trained to discriminate a prototype drug, such as an antipsychotic or an opioid. When a new drug of the same type might be superior, because it is effective at a lower dose, or has less, side effects, the new drug can be tested in animals that were trained to discriminate the prototype drug from the non-drug condition. The experiment determines what dose of the new drug is sufficient to cause the animal to make the same choice as the prototype drug.

TB: Which are the drugs you tested with the employment of this technique?

HB: Over the years, at the University of Pittsburgh, I tested a great variety of drugs. I began with barbiturates and alcohol. Two graduate students who earned the Ph.D. degree under my direction, Robert K. Kubena and R. Duane Sofia, were interested in research on marijuana. They did several studies on effects of Δ -9-tetrahydrocannabinol. Initially, in accordance with Dr. Raphael Mechoulem, who had originally synthesized the compound, we used the name Δ -1 tetrahydrocannabinol. An official consensus uses the name Δ -9 tetrahydrocannabinol. Our articles included a statement that Δ -1 is a different designation for Δ -9.

TB: So, you tested alcohol, barbiturates, THC with the employment of this technique. HB: Also morphine. One of my graduate students, Edward C. Krimmer, earned the Ph.D. degree under my direction and became my principal colleague for many years. Our research included morphine as the discriminative stimulus.

TB: Now, you worked mainly in animals. Did you do any research in humans?

HB: Not in psychopharmacology. I have given questionnaires to humans, but not related to drug effects.

TB: What did you study with the questionnaires?

HB: The questionnaires are designed to measure empathic choices in hypothetical situations. This research was done with Helene Borke, Ph.D., who is accompanying me at this meeting. She has a Ph.D. degree in psychology from the University of Chicago. The alternatives to empathic choices are emotional or rational choices. For example, if your five-year-old child has drawn with crayons on your wallpaper, how do you react? The empathic choice is, "I realize you wanted to experiment with something new." The emotional choice is, "I wish you had not messed up my wallpaper." The rational choice is, "I will let you use the crayons only on blank sheets of paper."

TB: What did you find?

HB: We found nothing clear-cut or definitive, as yet. The choices are highly specific to the situation. The questionnaires, thus far, have been given to students at Community College of Allegheny County, near Pittsburgh. Older students choose the empathic response more often and younger students choose the emotional response more often. We expected that females would choose the empathic response more often, but there is very little difference from male students. We did find more empathic choices by females in the initial version of the questionnaire. Choices in that version were general traits not associated with a specific situation, such as "I am usually

sympathetic" or "I am usually enthusiastic" or "I am usually logical." I believe that the specific hypothetical situations are more valid measures of empathy.

TB: Are you still involved in this kind of research?

HB: Yes, I have constructed many successive versions of the questionnaire.

TB: Are you still involved in research in psychopharmacology?

HB: Not now. Several years ago, for a couple of years, I participated in a project on alcohol effects with Seymour M. Antelman, Anthony R. Caggiula, and David J. Edwards. In 1991, I was co-author of S.M. Antelman, A.R. Caggiula, D. Kocan, S. Knopf, D. Meyer, and D.J. Edwards, in an article on "One Experience with 'Lower' or 'Higher' Intensity Stressors, Respectively Enhances or Diminishes Responsiveness to Haloperidol Weeks Later: Implications for Understanding Drug Variability," that was published in *Brain Research*. In addition, I suggested ideas for developing novel apparatus or techniques, but they were not used. TB: You suggested developing novel apparatus or techniques to measure what?

HB: Spontaneous activity of laboratory rats, I proposed a dark, enclosed place to measure the amount of time the animals ventured into the larger, illuminated arena. That apparatus might be a useful measure of the degree to which spontaneous motor activity measures boldness instead of fear. Conventional tests of spontaneous activity measure stimulation instead of depression of motor behavior.

TB: Why did you decide to close your laboratory?

HB: My relinquishment of my animal laboratory is partly due to other interests, including the research on empathy I have described, in addition to difficulty and expense of maintaining a laboratory animal facility. Another influence on me is the threat of animal rights activists, although I have never been personally attacked by these activists, and research on rodents is not a prime target.

TB: Have you served on any of the committees of ACNP?

HB: Several years ago I was a member of the ACNP committee on laboratory animal experimentation. My former dissertation advisor and colleague, Neal Miller, has been defending laboratory animal research very effectively and eloquently. As a laboratory animal researcher, I was obviously interested in that topic.

TB: When was that?

HB: I became a member of ACNP, in 1986. Therefore, it must have been within the last twelve years. It was probably six or eight years ago.

TB: Haven't you been involved in some editorial work?

HB: Emphatically, yes. I believe one of my major credentials for ACNP membership and a major personal contribution to psychopharmacology was my function as field editor for laboratory animal behavioral research for *Psychopharmacologia*, beginning in 1974. My title was Managing Editor, and I became Coordinating Managing Editor for the other Managing Editors in the western hemisphere of the world. Subsequently, the Journal's name was changed to *Psychopharmacology*. I served as Managing Editor until 1991, for 18 years. I received more than two thousand manuscripts. More than a thousand of them were published in the journal. My predecessor was Conan Kornensky and my successor is Klaus A. Miczek. They are both members of ACNP. I regard Klaus Miczek as an especially excellent and effective editor. I felt glad when I was relieved of that task, but I enjoyed doing it, and I believe that it was an important contribution to the field.

There is some equivalence between a journal editor, who helps to choose which manuscripts are published, and a member of a research review committee, who helps to choose which research-grant applications are funded. I have had experience with both roles, much more extensively as a journal editor than as a member of a research review committee. Some people probably place greater value on membership of a research review committee, because they participate in determining the expenditure of thousands of dollars and the careers of the investigators who apply for research grants. I preferred journal editing, partly because the decision was primarily mine. I sent the manuscripts to two reviewers. I was strongly influenced by their opinions, but it was primarily my judgment and opinion that determined publication. I also had the opportunity to improve the paper because my usual procedure was to specify needed changes and send the paper back to the authors, if I believed the research report could be accepted. I very seldom accepted a manuscript without requesting revisions and corrections. In contrast to the decisions by an editor, a member of a research review committee negotiates or debates with other members of the committee. Another difference is that a grant application usually contains grandiose statements about what wonderful research is going to be done, but the proposal is not a reliable prediction of the quality of the prospective research. A manuscript submitted to a journal is a product of the

research. Its quality is usually much better. Therefore, I prefer to read a manuscript submitted for publication than to read a grant application.

TB: You have been all through your professional life with universities. What proportion of your time did you spend teaching?

HB: The minority of my time was teaching. When I started at the University of Pittsburgh, in 1963, I was as a full time researcher. I continued to be obligated to do full time research as recipient of a research scientist development award for two five year terms from 1967 to 1977. Actually, I believe that I did more teaching during those ten years than before, or after. I taught one third of a course for undergraduates, a general pharmacology course, and I gave lectures in other courses. I also taught two graduate courses. They were on biomedical statistics for many years, and for several years, on behavioral psychopharmacology. Subsequent to 1977, I have given less than ten hours of lectures per year. They were in team taught courses. Therefore, my teaching load has been negligible. I hope that I have contributed enough, by my research and journal editing, to make up for the fact that I did so little teaching. I have not been asked to do any more teaching.

TB: You also had several graduate students, didn't you?

HB: I was the principal advisor for five students who earned the Ph.D. degree. In 1970, I was the principal advisor of Robert K. Kubena; in 1971, of James L. Perhach and Duane R. Sofia; and in 1974, of Edward C. Krimmer and Tsung-Ming Shih. I have also served as a member of the Ph.D. dissertation committee for many additional students, including several in the Psychology Department in the University of Pittsburgh and in the Pharmacology Department in the Medical School of the University of Toronto, in Ontario, Canada.

TB: On this note we should conclude this interview with Dr. Herbert Barry, III. Thank you, Herb for sharing this information with us.

3. FRANK M. BERGER

TB: We are in Nashville, Tennessee. It is April 6, 1999, and I have the pleasure to interview Dr. Frank Berger⁵ for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Dr. Berger's name is linked to the discovery of meprobamate, which was one of the major events that triggered the development of psychopharmacology. Dr. Berger is one of the pioneers of the new field. But let's start from the very beginning. Could you tell us when and where you were born, something about your education and early interests?

FB: Thank you for your generous remarks. I was born, in 1913, in Pilsen, the famous beer town, located in what is now called the Czech Republic. At the time I was born, Pilsen was in the Austrian-Hungarian Empire; after 1918, it became a city in Czechoslovakia, and today, it's in the Czech Republic. That's the place where I grew up; I went to Czech schools, and eventually to the German University, in Prague. My primary interest was to do medical research.

TB: Did you actually do any research while you were a medical student?

FB: Yes. I found some of my teachers inspiring and worked with Professor Kahn on the local action of hormones. I also did research in bacteriology and developed a treatment for cystitis.

TB: Was your treatment for cystitis used in clinical practice?

FB: A pharmaceutical company became interested and bought it.

TB: So, it was used?

FB: It's still being used.

TB: How old were you when you developed that new treatment?

FB: I was about 22 years old.

TB: So you made your first discovery while you were still a medical student. What did you do after graduation from medical school?

⁵ Frank Berger was born in 1913, in Pilsen, Moravia (now the Czech Republic) and received his M.D., in 1937, from Charles University, in Prague. He began his professional career as a bacteriologist in his native country, but left Czechoslovakia, in 1939. He worked in the laboratories of the British Drug Houses in London and then at the Department of Pediatrics, University of Rochester. Thereafter, he occupied leadership positions at Wallace Laboratories of Carter Products in the USA. In 1972, Berger resigned from Carter Wallace and active research. He died, in 2008, in New York City. He was interviewed in Nashville, Tennessee on April 6, 1999.

FB: I accepted a position at the Czechoslovakian National Institute for Public Health. It was the Czechoslovakian NIH, and I did primarily bacteriological research, related to typhoid and paratyphoid. It was just discovered that the various paratyphoids can be typed and identified.

This was of great public health interest, because of the many kinds of dysentery and food poisoning. I was fortunate I could do research in bacteriology as a medical student and continue research in that field after graduation.

TB: So your first career was in bacteriology. Do you have any publications from that research?

FB: All my findings were published.

TB: When did you have your first publication?

FB: In 1935.

TB: So you had your first publication when you were 22 years old?

FB: And I had a publication almost every year after that.

TB: So you had several publications by the time you left Czechoslovakia. How old were you when you left?

FB: I left Czechoslovakia in 1939, when I was 26 years old.

TB: Could you tell us about the circumstances when you left and something about your family?

FB: Hitler occupied Czechoslovakia, in 1939. My mother was Jewish, and people who were of Jewish origin were not welcome any longer. I expected that this would happen, so I was ready to leave. I had an uncle in the United States, who I persuaded to send affidavits for myself, my girlfriend, my parents, my brother, and my sister. With his guarantee, we had our passports and visas that permitted us to enter the United States. Hitler came on the 14th of March, I believe. I married my girlfriend on the 15th, and on the 16th, got on the train with her and my brother and left for America. My sister and parents couldn't be persuaded to leave. We were not allowed to take any money with us, only what we could carry in our bags. But I was happy to go. We left by train to Holland, where we intended to board our ship to America, but when we arrived we were told that we could not board ship because the United States declared all visas issued to Czechoslovakian citizens invalid. We were also told that we could stay in Holland for one week, and if we didn't find a place to go, we would be deported back to Czechoslovakia. We were fortunate in obtaining entry to the United Kingdom, through the generosity of an English lady, whom I never met. She

was a Quaker. As soon as we arrived in England, I wanted to thank her, but she discouraged me. It is thanks to her, that I'm here today.

TB: What did you do after you arrived to England?

FB: I looked for a job but had many difficulties. My English was very poor, because in the Czech schools we weren't taught English. I also discovered that my wife was pregnant. I went through a period when I had no money and no friends. I didn't want to put myself on public support, so I lived from what I got at soup kitchens and at the Salvation Army. To be accepted by any of the support organizations, I would have to declare myself Jewish, Communist, or Roman Catholic. And, I refused to do that. I prided myself as a human being. I never belonged to any of these organizations. I felt I could not adopt a teaching in which I didn't believe. But, something had to be done for my wife, and the Jewish Center accepted her. They said she could stay there and do whatever she could to make herself useful. Incidentally, she was not Jewish. It was generous of the Jewish Center to accept her. Her life was not in danger because of Hitler; she left because she wanted to be with me. I was looking for a job but some of the offers I got, such as driving a bus in London, I didn't like. So I slept on park benches, and usually ended up at three o'clock on the bricks of a prison floor, which sometimes I felt was a present. I always applied for solitary in prison, but I rarely got it. There were more and more refugees on the streets of London, and the British government decided they would arrange for a place to put us.

They decided on Broadstairs, in southeastern England. I don't know how many hundreds of refugees were there. We were held captive and got a little pocket money to buy food that we cooked together. I was a physician at the camp, working with an English doctor who was in charge, taking care of the medical needs of the refugees.

TB: That was in 1939?

FB: Right. Then one day in September, the war started, and soon after the Germans occupied France and started bombing England. So we had to be cleared out from the buildings. People from that whole area of Southeast England had to be moved to various other regions. I was moved with my wife to a suburb of London during the air raids and big fires and did some limited medical work in the hospital in Kingston. At that time, refugee physicians were not permitted to do independent medical work. That changed early, in 1941, when we were permitted to apply for a position as a physician.

TB: What position did you apply for?

FB: By that time I could speak English and the position I applied for was in a hospital for infectious diseases, in Manchester. It was affiliated with the University of Manchester with about 800 beds.

TB: Working in a hospital for infectious diseases was in keeping with your background in bacteriology.

FB: Yes. That was one of the most interesting periods of my life. I learned a lot about infectious diseases while there. During that time, there was an epidemic of diphtheria, in Manchester. I don't think I'd ever seen a case of diphtheria before. Mostly babies, one year old or less were afflicted.

TB: We don't see diphtheria any longer.

FB: Strangely enough, some of these babies were vaccinated, but the vaccine was not very effective. Some nights, several babies were admitted. The only chance they had for survival was to receive intravenous antitoxin. It's the most difficult thing to find a vein in a one-year-old baby, and it's very depressing to feel that unless you find a vein, the baby is going to die. And, many, many of them did. The most horrible thing I had to do was inform the parents the next morning what happened. These parents loved their children. This was the time I became an agnostic. I felt if the good Lord permits this, a man of character should have nothing to do with that good Lord. There were many cases of polio at the hospital, as well. We had ten iron lungs going at all times. Polio was a hopeless disease. Nothing was known about it and nothing could be done. We also had patients with tuberculosis, and nothing could be done for them either. We had an epidemic of meningitis that started in young girls recruited into the British Army.

TB: What year was that?

FB: In 1943.

TB: I suppose you had to work day and night in the hospital.

FB: Oh, yes. It was a strenuous job but it was important to do it and I'm glad I had that experience.

TB: It was probably the last opportunity to see those diseases in the Western World.

FB: Polio, diphtheria, tuberculosis are now virtually eradicated. Of course, I could not do any research in those years. Then, in 1946, I saw a position in the east region of Yorkshire, in a place called Wakefield, affiliated with the University of Sheffield. They had large laboratories and I applied for a position as a bacteriologist. I was accepted and given some routine duties, like supervising bacteriological testing, but I was also able to do some research.

TB: So you could pursue again your interest.

FB: Professor Sathalet, the head of the laboratory, was a forward looking intelligent man with broad interests. It was a pleasure to work there. A lot of research was going on with penicillin and I became interested in that field. The problem to be solved with penicillin was extracting it from the liquid in the bottles it was grown in. The liquid had to be acidified, and as a result of the instability of the pH, 90% of the substance was lost. I felt that while one lost so much of the active substance, no progress in the use of penicillin could be made. So, I devised a simple way for extracting penicillin at a neutral pH by turning it into a salt.

TB: Did you publish your method?

FB: Yes, I published it in *Nature*.

TB: Was this your first publication in English?

FB: Yes. At a time people didn't want to publish any article that might help the enemy. But I resisted keeping it a secret.

TB: You felt that the benefits of your discovery should belong to everybody?

FB: Sure. So many lives depended on surviving pneumococcus and streptococcus infections.

There was nothing else to treat them. I published it in *Nature*, I believe, in about 1944.

TB: What happened afterwards?

FB: At that time, all the pharmaceutical firms concentrated on producing penicillin. Because of my publication, I was offered a job by British Drug Houses (BDH), to work on their penicillin project. I joined in 1945, after they made an offer which was financially satisfactory, better than the university.

TB: Where were they located?

FB: In London. When I arrived we still had "doodle bugs," pilot-less bombs that exploded. The war was still on. I remember when the war ended we all went from the laboratory to Trafalgar Square to celebrate.

TB: What was your position at BDH?

FB: I was working in the research department. BDH was one of the most important firms at that time in England, but the research department was not large. My task was to develop a way to protect penicillin in solution from Gram-negative penicillinase producing bacteria. It was to find

a nontoxic agent which killed Gram-negative bacteria. One such agent was phenyl ether of glycol, called phenoxitol.

TB: So, you identified phenoxitol as a potential substance to protect penicillin from Gram-negative, penicillinase producing bacteria?

FB: Yes, but when I gave phenoxitol to mice, I found it too toxic. So we prepared other substituted phenols to achieve our objectives. One substance that worked very well was called mephenesin. With mephenesin I noted that it produced reversible flaccid paralysis of voluntary skeletal muscles, while the animals were fully conscious. It was something I had never seen before.

TB: So, you recognized you had a drug that was pharmacologically different from any of the drugs you were familiar with.

FB: I recognized I had a new medication and the substance was non-toxic. But, by that time, nobody was interested in finding a substance that would protect penicillin.

TB: Why was that?

FB: A brilliant scientist discovered a way to preserve penicillin by freezing the solution and drying it. So, nobody was interested in my penicillin preservative anymore. But I remained interested in the unusual pharmacological effects of mephenesin and proposed to the management of BDH that we do some more pharmacological work with the drug to find out what was behind its unusual effects.

TB: What did you find?

FB: I found that administration of mephenesin in appropriate dosage by the oral or parenteral route in mice, rats, guinea pigs, and other small laboratory animals produced muscular relaxation. With paralysis of all voluntary skeletal muscles, the animals lost their righting reflex so that they were unable to turn over when put on their back. Their muscles were limp and completely relaxed. Yet the animals appeared conscious. Their eyes were open and they appeared to follow what was happening around them. The corneal reflex was present and they were able to respond with some movement to painful stimuli. During paralysis, spontaneous respiration, although largely abdominal, was preserved. The heartbeat was regular and there were no signs suggesting an involvement of the autonomic nervous system. After paralysis was present for minutes or hours, depending on the dose, there was spontaneous and complete recovery to the state prior to administration of the drug.

TB: Did you have any idea about mephenesin's mode of action?

FB: We found that the monosynaptic knee jerk was not affected, whereas the flexor and cross extensor reflexes were considerably diminished. Since both the flexor and crossed extensor reflexes have interneurons between the afferent and efferent component of the reflex arc, these findings indicated that mephenesin blocked interneurons. The first possibility regarding the use of mephenesin was general anesthesia but the drug was hemolytic when it was given intravenously. I described mephenesin in my first publication as a muscle relaxant and noted its tranquilizing properties.

TB: What is the essential difference between the mode of action of barbiturates and mephenesin?

FB: The effects of mephenesin are on specific areas of the brain, whereas, barbiturates have an overall action. After my first paper on mephenesin was published, I became interested again in going to America. So, I applied and got a visa, and went to the states, in October 1947.

TB: This happened after you discovered the unique muscle relaxant and tranquilizing properties of mephenesin. Am I correct that you published your findings in England before you left?

FB: Yes, in the *British Journal of Pharmacology*, in 1946. The discovery of mephenesin's unique pharmacological action was made in 1945.

TB: What was the response to your paper?

FB: There were a lot of reprint requests. So, I corresponded with some people in the United States and they encouraged me to go to America. I needed some encouragement, because at that time it was not permitted to prearrange a job before arriving to the United States. You had to swear that you made no prearrangement. So, I didn't make any, but I did prepare a list of people who requested reprints. I arrived in America in October 1947 and called or wrote to the people on my list and told them that I was in America and looking for a job.

TB: Am I correct that you arrived with your wife and your older son, Franklin.

FB: Franklin was born, in 1949. It was just my wife and I.

TB: Did your brother stay in England?

FB: My brother returned to Czechoslovakia, in 1945, after the liberation. He went back, claimed his inheritance, and started a new life with the intention to stay in Czechoslovakia. It didn't do him much good, because after the communists took over the country, everything was taken away. Then he came to America.

TB: Did you have any problem with the immigration authorities when you arrived?

FB: I had no problem. My uncle sent me the necessary papers. But I had to swear that I didn't have a job. There was another limitation at that time; you couldn't bring more than three hundred dollars with you. So, I didn't have much time to find a job. But I got in touch with the people on my list, and one of them, Dr. Bass, who is here in Nashville, invited me and offered me a job. He was most kind to me. At that time, he was professor of pharmacology at the University of Syracuse, in New York.

TB: So, it was Allan Bass first who offered you a job.

FB: Several people who read my paper knew I needed a job. He was one. There were others, for example, Dr. Schlesinger at Columbia, Dr. Schwartz at Rochester, and Dr. Blancard at NIH.

TB: Your arrival in America was different from your arrival to England.

FB: Absolutely. I was a little short of cash, but I had a job in less than a month.

TB: It was good that people responded so promptly.

FB: I was much better known by the time I arrived here. People here knew about my work with mephenesin and were very friendly and generous. It was very different from my arrival in England.

TB: What was your first job in the United States and how did you select it?

FB: I knew nothing about the American system, but I had a very good friend here, George Blancard. He is an American by birth, but we went to medical school together in Prague. We became friends at medical school and after he returned to America, he worked at the NIH. It was George Blancard, who advised me to accept a university position in Rochester, New York. I did and enjoyed it.

TB: How long did you stay in Rochester?

TB: Till the end of 1947. I was Assistant Professor of Pediatrics, but my main interest was research. I wanted to continue my research with mephenesin because I was fascinated by its unusual effect on the central nervous system. I needed some very expensive equipment, electroencephalographs and oscilloscopes. I was advised to apply for it. So I did and was very fortunate; I obtained all the things I thought I needed. They were obtained through collaboration with the department of chemistry, where people made compounds for me. My aim was to produce something that would do the same that mephenesin does, in smaller doses and for a longer period

of time. So, the first thing that I did in Rochester was to find out why mephenesin is so short acting

It was one of the shortest acting drugs known. When you swallow a tablet, you can show the presence of it in the urine in less than half an hour. So, a chemist in the department produced various compounds and I let people help me determine which part of the molecule of mephenesin makes the drug short acting, so it could be blocked. My objective was to modify the molecule, so that the action was more prolonged. After it had been identified that it was the part of the molecule attacked by OH groups, the plan was to prepare compounds where the OH group would be blocked. These compounds were prepared and evaluated but, as a whole, they didn't act much longer than mephenesin, or if they did, they were pharmacologically not more powerful. Meanwhile, I thought I'd get into studying mephenesin's action in human beings, so I was looking for somebody to prepare a supply of mephenesin tablets that I could give to patients. Ultimately, it was done by Squibb. I had a clinic of people with neurological and psychiatric disorders on whom I tried tablets. I tried it first on cerebral palsy patients and found that, in spite of the short duration of action, it did relieve to some extent, not only their muscle spasms but also the involuntary movements. I tried it in Parkinson's disease and found it also affected, for a short time, their symptoms.

TB: Didn't you have some experience with mephenesin in humans from England?

FB: I knew that mephenesin was well tolerated. I tried it on myself and discovered it was safe.

TB: Wasn't mephenesin on the market in the UK?

FB: Yes, in Britain.

TB: But not here?

FB: Not here, and even in Britain, only for intravenous use, and that was just impractical. There's a constant risk of hemolysis giving IV mephenesin, but it seems to be safe orally. I had about 200 patients with cerebral palsy, Parkinson's disease, and all kinds of involuntary movements and I tried it in many of them with fair results. I published it in the Journal of the American Medical Association. Very much to my surprise, the paper was accepted and created great publicity. It was written about in newspapers, in 1948, and Squibb managed to get mephenesin approved by the Food and Drug Administration. It came out on the market and became their best-selling drug.

TB: It was a gift to Squibb; it seems you did all the work. All that Squibb had done was get it approved and marketed. At this point you were still employed by the University of Rochester?

FB: I was Professor of Pediatrics and my position was secure, because when you are with a university, you have to publish a lot; during 1948 or 1949, I published about 11 papers. Because of the newspaper publicity and the great commercial success of mephenesin, I started to be approached by pharmaceutical firms. And I became receptive.

TB: Did Squibb approach you? They made a fortune with mephenesin.

FB: Yes, they did. I made it clear to Squibb that I would be happy to work with them and they asked me what I would like as salary. I said it just has to be better than what I'm receiving now, which is \$5,000 a year, but I'm more interested in participating in the fruits of my labor. If I develop a successful drug, I would expect that you pay me a royalty. As soon as I mentioned that they said that's not done in this country.

TB: You'd already handed them a gift!

FB: They didn't look at it as a gift, you see. They mentioned I had published on it in the UK and my firm, British Drug Houses had a patent on it. I didn't know anything of American patent law, which is much more generous to a layman who takes out a patent, but in England, a patent is automatically assigned to the firm for which you work. In any case, Squibb thought if anybody doesn't feel happy, they could sue. Then I was offered other positions but there was only one, Carter Products that gave me hope. Carter Products had a small ethical subsidiary, called Wallace Laboratories; Carter itself was powerful and well known for Carter's Little Liver Pill and for a deodorant stick.

TB: So, Carter was the only one that let you participate?

FB: They were the only one and my friends in Rochester were shocked when I told them that, of all the firms, I would join Carter's Little Liver Pills. In June 1949, I became their research director. I was fortunate in finding a very capable and intelligent chief chemist, Bernard Ludwig, who was happy to prepare all kinds of compounds for me. They didn't have a pharmacological laboratory or an animal house, so all that had to be built. While it was being built, Dr. Ludwig prepared the compounds.

TB: So, the research department was basically the two of you?

FB: Each of us had assistants, but it was just he and me. We started experimenting and soon came up with an acceptable compound, which we called meprobamate, which was a carbamate ester of glycerol ether. We came up with that in 1950, and a patent was applied for meprobamate and related compounds in the same year. In the original patent, the main claim was anticonvulsant action and that was picked because it was easily identified and accurately measured. But, we also did some pharmacological studies in which we identified the dose of meprobamate which produces relaxation of voluntary muscles.

TB: How did you do that?

FB: One method was insertion of needles in the brain and determining the differential effect of the substance between cortex and thalamus. Tranquilizers have a selective action on the thalamus and no effects on the cortex. The best compound is the one that has an effect on the thalamus, without an effect on the cortex. This method was used in testing ten or twelve compounds. We had over three hundred and had to sort them out.

TB: By screening?

FB: We sorted them by their potency: (1) as an anticonvulsant, (2) of producing paralysis of voluntary muscles, and (3) on interneuronal reflexes. We chose the one that was most potent and least toxic.

TB: Was this meprobamate?

FB: We screened down to 10 or 12 compounds first, which we then tested in cats, and picked a compound that didn't affect the knee jerk but affected the flexor reflex and, at the same time, had a synchronizing effect on the discharges coming from the thalamus without affecting the cortex. The best we could come up with was meprobamate.

TB: What happened with the other compounds?

FB: We worked with all of them later. One, which was a much stronger anticonvulsant, was developed as an antiepileptic.

TB: Maybe you'd like to get back to that later.

FB: The first thing with meprobamate was to establish its lack of toxicity. We had an outside agency making meprobamate for us and it was not easy to find one. Finally, I persuaded Bob Milano, the president of a small chemical plant, in New Jersey, to set up facilities for manufacturing the drug. It was the company that manufactured the first tablets of mephesisin for

Squibb. I told them I was the man who discovered mephenesin and I had something better; so, they did it at an affordable cost. We needed a lot because I would not let anybody give it to a human until we had finished one year of toxicity in several species, although that was not required at the time by the Food and Drug Administration. I just did it because I wanted to sleep at nights.

TB: If I remember, you said that you tried mephenesin on yourself.

FB: Yes, but I knew already that mephenesin was harmless.

TB: So you did one year toxicity studies in several species. How did you derive the dose? FB: We had a clinician try it. We tried a hundred milligram tablets and ended up with four hundred milligrams, which looked effective. Then, I had a psychiatrist, in New Brunswick, who was helpful trying it on patients and another physician, in Florida, who confirmed it was an antianxiety drug.

TB: What kind of patients did they study?

FB: Most were ambulatory, psychoneurotic, hyperactive individuals who had psychosomatic symptoms.

TB: Meprobamate was developed in the first half of the 1950s?

FB: Yes. But I couldn't persuade Carter to invest the money the way I wanted, and even by 1954, they didn't stand firmly behind it. To introduce a drug, you have to produce a lot of it. It is to be shipped to places and you have to let physicians know you have it. All of that cost, even at that time, more than a million dollars. A million is nothing for a pharmaceutical firm, but CarterWallace was not willing to invest. What they did do, because there was no anti-anxiety agent available, in 1954, they hired a Gallup poll to find out what doctors were doing for anxiety. They wanted to know that before investing money. So the Gallup poll found that out. I had a wonderful technician by the name of Lynes, who was very good at handling monkeys. So we decided we'd see what meprobamate would do to Rhesus monkeys because they're wild and difficult in the laboratory. If you meet them in India, they are very kind and gentle. We gave meprobamate (Miltown), barbiturates, and two or three other drugs to Rhesus monkeys, observed their behavior before and after, and made a movie. A monkey after the barbiturate was flat out. A monkey on nothing had to be handled with asbestos gloves. And a monkey, after Miltown, became friendly and nice, so you could take off the asbestos gloves and shake hands. I decided to show that movie at the Federation meetings, in San Francisco, in 1954. Some members of the audience from Wyeth

told me that after the drug is tested in humans and becomes available, we could license it to them. So I arranged for Wyeth to get the license for meprobamate.

TB: By that time you had done a series of clinical investigations?

FB: Yes, and I was in the process of getting it through the Food and Drug Administration. We made an application, in 1954, and, in June 1955, it was approved. Meprobamate became tremendously popular. Maybe the name, Miltown, helped.

TB: How did you get to the name?

FB: We gave each compound we studied the name of a New Jersey town. The only one which showed good results was called Miltown. One of the doctors, Dr. Borrus, wrote a paper on his findings, that he published in the Journal of the American Medical Association, in which he referred to the substance as Miltown.

TB: What year was that?

FB: That was in 1955.

TB: Could you tell us something about Dr. Borrus' study? How many patients were involved?

FB: Approximately 150, maybe 200.

TB: What kinds of patients were involved?

FB: Those were all psychoneurotic patients.

TB: If I remember, Leo Hollister was working with meprobamate in schizophrenic patients. What about Karl Rickels?

FB: He had a mixture of patients.

TB: By the time the drug was approved by FDA, I suppose it was clear that it was for patients with anxiety disorders?

FB: Exactly.

TB: Then, the drug was marketed by Carter Wallace and Wyeth simultaneously?

FB: Wyeth called it Equanil and they sold twice as much as we did, because doctors preferred the name Equanil to Miltown. But Miltown broke the ice and there was a lot of joking about it. Milton Berle on television called himself Miltown Berle.

TB: We are now in late 1955 and 1956. Meprobamate is available for clinical use as Equanil and Miltown in the United States. What about the rest of the world?

FB: Equanil was sold by Wyeth all over the world. Wallace Laboratories became big and Carter Products changed its name to Carter-Wallace. Then they wanted to be recognized on the Stock Exchange and I helped them do that.

TB: When did this happen?

FB: In 1956. That was a very interesting experience.

TB: Didn't you become president of Carter Wallace? When was that?

FB: In 1955. When I took over Wallace Laboratories, the annual sales were \$80,000. In 1956, the annual sales were about \$200,000,000.

TB: You created not only a drug but also a company!

FB: Yes, a company that was listed on the New York Stock Exchange.

TB: Did the company grow as years passed?

FB: I gradually built it up to about a hundred people. I had plans for other products; I never forgot my love for microbiology. I had about thirty or forty people just in that field. The basic problems that interested me there was that not everybody who gets infected gets sick. Not everybody who comes in contact with typhoid or tuberculosis develops a disease. Why is that? TB: Later on that was to become your primary interest. But during the late 1950s and even in the 1960s you did extensive research with meprobamate.

FB: Yes.

TB: Could you say something about that research?

FB: I wanted to know, for example, how it affects normal individuals. So, I got some people from the Mental Health Institute at the University of Michigan, who were interested in Milltown, like Ralph Gerard, James Miller and Anatol Rapoport, to carry out an extensive program with the drug.

TB: So, Ralph Gerard was involved.

FB: Yes. He was the Director of the Mental Health Institute and his group found you don't feel any better if you're taking Milltown, unless you are anxious. They also studied the effects of meprobamate on driving skills.

TB: There was an important meeting on meprobamate in New York?

FB: That was at the New York Academy of Sciences, in 1956. By the middle of that year, over a hundred papers had been published on the effects of meprobamate. It was a world in which tranquilizers like meprobamate were used, abused and misused. I felt it was high time to arrange

a conference to review the state of art about the use of tranquilizers and find out what writers and philosophers also think of the new era in psychotropic medications. I thought it would be a good idea to invite the Huxley brothers; Aldous Huxley, a great writer who was always very much interested in substances affecting the mind, and Julian Huxley, a biologist and philosopher. They both agreed to speak at that conference. We also had leaders in various professions; Ralph Gerard, one of the leading neurophysiologists, Jim Miller a Professor of Psychology and Psychiatry, Harry Beckman, the President of the American Pharmacological Society, and many others. We had this two-day conference and published the highlights. The meeting also had another purpose. At that time, many doctors and most laymen didn't differentiate between antianxiety and antipsychotic drugs, and I tried to make it a point at the meeting that there are differences between these new drugs. On the one hand you have substances like chlorpromazine and reserpine with an effect on the autonomic nervous system which affect severe mental disturbances, such as schizophrenia, and control hallucinations and delusions. And on the other hand, you have substances such as meprobamate or mephenesin that do not affect the autonomic nervous system but are effective in relieving tension and anxiety. That was an important point to make. And another important point was that anxiety is not a normal condition.

TB: Could you elaborate on your thoughts about anxiety?

FB: There is sound evidence that indicates that anxiety is not a normal condition. Many people and even psychiatrists confound anxiety with fear, as for example if an uncontrolled automobile runs towards you. Anxiety is a dimension of the personality that affects performance that makes you less effective, and less capable of dealing with problems of living. Probably, most important is that anxiety can be affected by certain drugs. Anxiety is incapacitating. It's true one might perform a little better in a stressful situation when taking a test, if the adrenaline mobilized makes one more attentive, receptive, and responsive. But if one is also anxious of not knowing enough to pass the test, which interferes with performance, you don't perform as well.

TB: It is an important distinction.

FB: This distinction was shown very clearly in psychological testing by Dr. Cattell of the University of Chicago.

TB: Did you collaborate with Cattell?

FB: He arrived at this distinction on the basis of his studies. I came up with it completely independently. When I learned about his work, I asked him to study meprobamate in human beings.

TB: Cattell has become quite well known for separating normal from pathological anxiety with the employment of factor analysis. I suppose Cattell's findings might have been useful also in marketing. How much were you involved in the marketing of your drugs

FB: I enjoyed the experience of marketing, but I felt that it should be done in a dignified way. Meprobamate was always a prescription drug, and in my opinion, the task of advertising is to inform the doctor that it exists by sending them information about its mode of action. I am strongly opposed to the usual form of advertising by detail men. I feel that physicians should go to the real sources of the information about the drugs they are using and should not get acquainted from laymen who have vested interests. The proof that your product is good is the proof that it's needed.

TB: And meprobamate proved itself by becoming the number one drug in sales.

FB: The Company became unbelievably prosperous. The profit margin was far bigger than anyone expected. Mr. Kefauver was a person in Congress, who was running for President. He called most presidents of the pharmaceutical companies to testify before his committee and wanted to show that the industry makes too much profit by doing things improperly. I was one of the people he subpoenaed to testify. I learned something when he cross-examined me that I didn't know, namely, that ours was the most prosperous company at that time in the country. TB: Did the people who owned Carter Wallace recognize you made their company the most prosperous in the country? Did they compensate as you deserved?

FB: At the time I was hired, in 1949, long before meprobamate appeared on the market, we had signed an agreement that I was entitled to a royalty of one percent on sales up to seven and a half million. There were no sales of any kind in that range at the time. I made forty thousand dollars a year and I thought that was a lot of money. It was. But when meprobamate came, it sold more than \$200 million a year, the profit, after costs and advertising, was more than thirty percent; 30% clear profit, \$60 million dollars. They had given me \$75,000 on a \$60 million profit. I thought I should do better than that. After lengthy discussions, I did a bit better. I got four percent, but I never managed to eliminate the seven and a half million upper limit.

TB: It was obviously a contract prepared by lawyers serving the interest of the owners of the company.

FB: At the time I signed the contract, I was new in the country and did not know how to protect my interests.

TB: It was, I assume, a good feeling that you created meprobamate and a company to sell it, because Carter Wallace was a very small company before meprobamate.

FB: Yes, it was fun to build a successful company. I added to some profits. And I developed another successful drug, Deprol, for depression. It was a combination of meprobamate and benactizyne. It sold quite well. Then, I developed Soma, which is still on the market and sells very well, without any advertising.

TB: When was Soma introduced?

FB: I think, 1958. If I remember correctly, it sold over 50 million a year.

TB: The primary indication for Soma is pain.

FB: It's a non-narcotic pain reliever. It is used for low back pain and that kind of conditions.

TB: Any important other drug after Soma?

FB: One was tybamate, another antianxiety drug.

TB: When was tybamate introduced?

FB: In the early 1960s.

TB: So it was introduced simultaneously with the first benzodiazepines.

FB: Yes.

TB: Was your experience in developing meprobamate used in developing chlordiazepoxide?

FB: Of course; the first benzodiazepines were synthesized by Dr. Sternbach in the 1940's, but Roche couldn't find any use for them before my description of the pharmacology of meprobamate came out, giving the technique to identify their action. They subjected all drugs made and patented by Roche to the screen I described and found several benzodiazepines effective.

TB: So, it was the pharmacological screen based on the effects of meprobamate that identified chlordiazepoxide as a potential drug for the treatment of anxiety. Was there any contact between you and Roche in that period?

FB: Not really. They were free to use the techniques I developed. I published them so that other people could use them. I feel that in medical science everything should be published. It's all right

to patent a compound because the patent lasts only for several years. It just gives an inventor a personal reward. But the technique used to make the invention should not be secret. It should be public so that other people could use it in order to develop even better drugs.

TB: Just about the time chlordiazepoxide and diazepam were introduced, the issue of dependency with meprobamate was raised. Could you elaborate on that?

FB: The benzodiazepines were promoted primarily by suggesting that they are less habit forming; but I don't think that meprobamate or any of the benzodiazepines are habit forming. In a sense, some people feel that coffee is habit forming. For most people it is. I would say that benzodiazepines and meprobamate are probably less habit forming than alcohol. After all, alcohol is habit forming in only 10% of the people who use it. We seem to talk about that 10% all the time and forget about the 90% of people who drink wine with each meal and don't become addicted. I think the Food and Drug Administration recognized that the addiction potential of meprobamate was exaggerated. Drugs that have the potential to be habit forming are put on Schedule II. Meprobamate has never been put on Schedule II. And the Food and Drug Administration and the Bureau of Narcotics looked at this issue carefully. On the other hand, many widely used benzodiazepines are on Schedule II. The most widely used benzodiazepine now is diazepam, which is primarily used as a sleeping pill. It is a typical benzodiazepine and, in the opinion of most people, it's one of the safest benzodiazepines. Yet diazepam is on Schedule II.

TB: So, as far as the FDA was concerned, meprobamate was actually safer than diazepam?

FB: The management of Carter Wallace made me feel I was at fault when I did not discover a product as successful as Miltown every two years or so. Unfortunately, not all of our projects succeeded. Bernard Ludwig made a very interesting series of compounds, and I asked myself, which one should be pursued pharmacologically. It also occurred to me that we should try to develop an agent that would prevent people dying prematurely because of heart attack or stroke. So, very early, long before the cholesterol lowering agents were introduced, I came up with compounds that could potentially prevent the development of arteriosclerosis. I was hoping we would develop one of these drugs, but the project never got off the ground because to test that kind of compound in humans is exceedingly expensive. So, it was not pursued with the intensity it should have been.

TB: What happened to those compounds?

FB: They were not patented, so nobody is interested in them anymore.

TB: So, they died because of lack of funds and interest?

FB: Then I moved to epilepsy, but management didn't want me to pursue it, because they felt there were not enough epileptics in the United States. They wanted me to find drugs with a big market. At that time, there were less than five million epileptics in the United States.

TB: Compared to the market of meprobamate that was a small market.

FB: The drug I discovered for epilepsy was first patented, in 1950. I did some studies in humans at Brown University. It was good but they just did not want it. But after I left the company, they revived it.

TB: When did they revive it?

FB: In 1980 or 1985. They combined it with another substance and got a new patent.

TB: What happened to it?

FB: After it was put on the market eight cases of agranulocytosis occurred and its use was restricted for cases of epilepsy that are not relieved by any other medication.

TB: Is it still on the market?

FB: Yes, but it's rarely prescribed. I also had a substance, called protodyne that would increase natural resistance to infections. But the substance was not developed while I was with the company. I started to have more and more problems doing my job.

TB: When did the problems start?

FB: I think the problems started in the late 1960s.

TB: What happened?

FB: Mr. Hoyt, the owner of the company was getting old and he told me, "You are a scientist. You still don't know how to read a balance sheet properly, and I want my children to have a safe and solid business. I want this company to run as a business and not like a charitable organization. I will ask a leading firm that advises management how to improve business and to investigate this whole set up." He hired a firm from Chicago that was well known in this type of study and they suggested I should be responsible only for the scientific part of the company. Everything else was taken away from me.

TB: This happened in the late 1960s?

FB: In the late 1960's and there was nothing I could do about it, because all the voting stocks were controlled by Mr. Hoyt.

TB: You created the company but did not control it.

FB: Right. I made it successful, I developed it from an \$80,000 to a \$200 million business, but I was defenseless. It was humiliating to me. Then my wife died, early in 1973, and I saw that this would go nowhere, so I resigned. An offer was made that in addition to my pension I would be paid \$100,000 a year on condition I did not work for any other firm but I refused.

TB: You wanted to remain your own boss. What did you do after you left?

FB: I left, in 1973, without any severance pay and I retired. I was about 59 years old, but I did not start playing golf. I became a consultant to many firms in Europe and in this country and participated in developing various immunological products.

TB: So you returned to your first interest, microbiology and immunology.

FB: Yes, but I never got enough financing to develop any of the products. By the time I got it going I was 65, and by the time, I had it all ironed out I was over 80. It's very difficult to get financial support at that age.

TB: Were any of your products for immunology developed?

FB: Carter Wallace developed protodyne later on.

TB: Did they involve you?

FB: They did it independently. But, they didn't do anything improper. They hired the best biochemist to purify protodyne. Later on, they dismissed all research personnel and stopped doing research. For a while, they tried to buy products, preferably ones that could be sold over the counter. Then, they went out of the pharmaceutical business. The only satisfaction I have is that Wallace's sale from pharmaceuticals went down from more than two hundred million a year to almost nothing after my departure.

TB: So it went down even below the level it was before meproamate.

FB: But they still prosper because they acquired Trojan condoms, shortly before the outbreak of HIV. This is now their main business.

TB: I remember, in the early 1980s, when we used to have lunch together in Geneva that you were still very busy consulting and trying to develop new products. Is there anything you are working on these days? You still have an office in New York.

FB: I have an office but I'm not trying to develop any new product. I will be 86 if I'm still alive in June, and it would be foolish to think I can generate the necessary money at my age.

TB: I know you have contributed chapters to some of the publications of CINP's history committee. Is there anything you'd like to comment on concerning the development of psychopharmacology in the past 50 years?

FB: In the 1950s, a new field, psychopharmacology was born with the discovery of antianxiety agents, and drugs for the treatment of schizophrenia and depression. Ever since, we have been sorting out and trying to improve things.

TB: Is there anything you would like to see happen in the future?

FB: We need some new breakthroughs in treatment. Research with neurotransmitters is very important but we're reaching the point where we know as much about neurotransmitters as we need to. We need to explore more intensively the biology of consciousness, learn more about the biology of falling asleep, not just what brain waves show, but also its chemistry. We need a new approach. The discoveries of the 1950s have been milked almost to death.

TB: Anything else you would like to tell us?

FB: I would like to say how greatly I appreciate your kindness and interest.

TB: I would like to thank you for sharing this information with us and conclude this interview with Dr. Frank Berger, one of the pioneers of neuropsychopharmacology.

FB: Thank you very much.

4. PHILIP B.BRADLEY

TB: This will be an interview with Professor Philip Bradley⁶ for the American College of Neuropsychopharmacology. We are in London. It is January 21, 2002. I am Thomas Ban. Let us start from the very beginning. If you could tell us first where and when were you born? Say something about your childhood, early interests, and education.

PB: Well, I was born in Bristol in 1919. My parents were quite poor; it was just after the end of the First World War. I had three brothers and two sisters, all of whom were considerably older than me, so I was the baby of the family. I went to a number of schools in Bristol. None of them would be well known, except possibly Cotham Grammar School where I took my matriculation examination before moving to Bristol University to study Zoology and Chemistry. For financial reasons, I could only get a place at university because I was given a grant from the Ministry of Education, which committed me to take a teaching post after graduation for, I think four years. However, the Second World War intervened and, because I failed a chemistry examination, I was obliged to join the army. At the time, science students were exempt from military service but, because I had failed this exam, I was no longer exempt. I spent six years in the army; and, at one time, I was posted to Brighton Technical College as an army instructor to teach electronics, which was a rather strange thing as I knew very little about it! I thought afterwards it might have been because I had studied Physics for my Higher School Certificate. So, I was teaching electronics to army students and had to learn it very quickly. After some two years, I went on to various other posts in the army, which involved working on radar, repairs and maintenance, and being in charge of radar and wireless workshops. Eventually I went back to Bristol to complete my degree. Because of this wartime experience in electronics, I then became interested in electrophysiology, and my research project in zoology was to record nerve potentials in insects.

TB: So, you continued your studies in zoology after you got out from the army?

⁶ Philip B. Bradley was born in Bristol, England, in 1919. He obtained a scholarship to study Zoology and Chemistry at Bristol University, and then, enlisted in the British Army where he mastered electronics via work in military radar and wireless. He earned his Ph.D. in Pharmacology at Birmingham University, where he studied the effects of drugs on the brain using electrophysiological techniques. He was very active in scientific organizations in neuropsychopharmacology throughout his career. He died, in 2009, in London, England. He was interviewed in London, England on January 21, 2002.

PB: Yes, I went back to finish my degree in zoology and chemistry.

TB: What year did you get your degree in zoology?

PB: That was in 1948, and I was then looking for employment. I was offered a post with the Colonial Service to work as an entomologist in East Africa. But, before I accepted that offer, I heard about a vacancy at the University of Birmingham in the Department of Pharmacology. They were looking for someone with my experience, and I had an interview with Joel Elkes and Alistair Frazier, who was then head of the Pharmacology Department. They offered me a post as a Research Fellow that I accepted. I was to work with Joel and study the effects of drugs on the brain, using electrophysiological techniques. Because of this, I took a course in electroencephalography (EEG) at the Burden Neurological Institute in Bristol with Dr. Grey Walter who, with Lord Adrian, had discovered electroencephalography. When I arrived in Birmingham, I started work on recording the electrical activity of the brain in animals and studying the effects of drugs on the EEG. At that time, there were not many drugs available with known actions on the central nervous system. So, I worked with atropine and physostigmine, which were used clinically at the time. The only treatment then for schizophrenia seemed to be sedatives and surprisingly, amphetamine, which had a dramatic effect on catatonic stupor. Shortly afterwards new drugs appeared. The first was, I think, LSD-25 and then we heard about chlorpromazine being used in Paris. This was a very exciting time, because we received samples of chlorpromazine, and Joel Elkes and his wife Charmian did the first clinical trial of chlorpromazine in the UK on schizophrenic patients, and I was a member of the team, doing the EEG's. My own work was primarily on animals. The idea was to develop techniques for recording the EEG in conscious, unrestrained animals which, at that time, I do not think had been done. It was Joel's idea for me to do the EEG course at the Burden, so that I would have some expertise in human EEG, and I used that subsequently. As well as taking part in the clinical trial of chlorpromazine in schizophrenic patients, I subsequently worked in collaboration with another psychiatrist in Birmingham, Peter Jeavons. We studied sedation threshold in schizophrenic patients, using the EEG. I was also invited to work with the neurosurgeons in Birmingham, who realized that recording the electrical activity directly from the cerebral cortex would be helpful in delineating tumors and epileptic foci on the exposed cerebral cortex. They did not have suitable equipment of

their own, and I used to trundle my equipment across to the hospital, where we sterilized the electrodes and other bits of equipment that came into contact with the patients.

Occasionally, I accompanied the neurosurgeon I was working with, Mr Eric Turner, to London to watch neurosurgical operations performed at the Maudsley Hospital. I also worked in collaboration with the Professor of Neurosurgery, Professor Brodie Hughes, recording the activity of single cells in the caudate nucleus, using stereotactic techniques. Brodie Hughes was interested in Parkinson's disease and, at the time, the condition was relieved by lesions of the caudate nucleus. It may sound illogical, but that's what we were doing. So I did have some experience using the electrophysiological techniques I had learned at the Burden, and I think that was quite valuable.

TB: Did you, by that time, develop your technique for recording electrical activity of the brain in unrestrained conscious animals?

PB: Yes, I had to develop the technology for animals, as up to then, recordings had been made in anesthetized animals and, apart from the effects of the anesthetic obscuring changes in the EEG, we also wanted to see the effects of the drugs on behavior. Therefore, I developed techniques for implanting electrodes in animals, in order to record the activity of the brain at the same time as observing the behavior. This was the work I did for my PhD.

TB: So your Ph.D. was in neuropharmacology.

PB: No, it was in pharmacology, as neuropharmacology, as a subject, did not exist then.

TB: Then, you got your Doctor of Science?

PB: That was later, and that was in Neuropharmacology. I got my PhD in 1952, at the time when Joel Elkes went off to spend a year to Washington. When he came back, he established a new department called Experimental Psychiatry, in which he took responsibility for the clinical work of the department, and I was in charge of the basic research, which also included neurochemistry.

TB: When did you do the research with barbiturates and amphetamines?

PB: That was in my PhD work.

TB: So, it was done between '48 and '52?

PB: That sounds about right. I worked initially with the drugs that were available at the time, i.e., atropine and physostigmine, to modify cholinergic function in the brain, and amphetamine and barbiturates to modify levels of consciousness. Later, when chlorpromazine and LSD became

available, I studied those, as well. In 1949, after Moruzzi and Magoun published their seminal paper on the reticular formation of the brain, I devised a series of acute experiments using lesions at different levels in the brain.

TB: Before telling us about your findings with lesions, could you elaborate on Moruzzi and Magoun's influential paper?

PB: They showed that stimulating the reticular formation, a diffuse structure in the tegmental region of the brain stem, comprising mainly short axon neurons and distinct from the main afferent pathways and the cranial nerve nuclei, with a relatively high frequency electrical stimulus (300 c/s) produced an arousal response as observed by changes in the electrical activity of the cerebral cortex.

TB: Now, what did you find with lesions?

PB: We were able to show that a lesion, which transected the midbrain cutting off the ascending influence of the reticular formation, blocked the stimulant effects of amphetamine; whilst, on the other hand, the effects of drugs with actions related to cholinergic mechanisms in the brain were unaffected by this lesion. So, we made some rather naïve predictions about the possible site of action of these drugs.

TB: At what levels did you have the lesions?

PB: I adopted the techniques of the Belgian physiologist, Bremer. One of the lesions was at the C-1 level in the spinal cord, which produced what he called, the *encéphale isolé*, an isolated brain but with an intact blood supply. This preparation showed periods of wakefulness and sleep, as judged by the activity of the cerebral cortex and responses to sensory stimuli. Another lesion was at the midbrain level which resulted in the *cerveau isolé*, or isolated cerebrum, and this preparation showed permanent sleep activity, presumably as the result of the removal of the ascending influence of the reticular formation. Our studies in these acute animal preparations showed that both transections of the spinal cord and of the midbrain did not modify the effect of cholinergic drugs, physostigmine producing an alert pattern of activity in the EEG and atropine, sleep-like activity, i.e., the reverse. However, transection at the spinal cord level appeared to block the alerting effect of LSD, and lesions of the midbrain blocked the alerting effect of amphetamine.

TB: What about chlorpromazine?

PB: Chlorpromazine seemed to have very little effect in these experiments and we were unable at the time to localize its effects to the brainstem.

TB: Didn't you find that chlorpromazine interfered with the response to afferent stimulation? PB: Yes. With my colleague Brian Key, who was a PhD student at the time, we devised an experiment in which we measured the threshold for arousal to electrical stimulation of the reticular formation and the threshold for arousal produced by afferent (auditory) stimulation. This work was done with acute *encéphale isolé* preparations and was supported financially by the US Air Force. We found that sedative drugs, such as the barbiturates, blocked the effect of the stimulation in the brainstem very quickly, whereas amphetamine had the opposite effect: it reduced the threshold, although this was very difficult to measure. We also tested the arousal response to afferent stimulation and found that chlorpromazine had little effect on the threshold for arousal produced by brainstem stimulation, but depressed afferent-induced arousal. LSD on the other hand had the opposite effect, facilitating the afferent-induced arousal. So we put forward the hypothesis that drugs, which affect levels of consciousness, probably act directly on the reticular formation either by stimulating or depressing it, whereas others, such as chlorpromazine and LSD, seemed to have less direct effect on the reticular formation but influenced the effects of afferent stimulation either by depression (chlorpromazine) or stimulation (LSD).

TB: Was anyone else, at the time, involved in similar research?

PB: Well, I think that some of the experiments that the Killams were doing in Los Angeles at the time might have been similar.

TB: How did the scientific community respond to your findings?

PB: Not very well, I must say. My recollection of presenting papers to the Physiological Society in London was that they were met with quiet acceptance, without much discussion. What we were doing was probably not considered proper physiology. On the other hand, because of my training in electroencephalography I was a member of the EEG Society and I gave papers at their meetings. These were received quite well by the audience that consisted largely of psychiatrists and neurologists and even some physiologists.

TB: You mentioned before that, while doing your research for your PhD, you worked with drugs like atropine and physostigmine. Did you do the research with anticholinergics that showed

dissociation between the changes in the EEG and behavior, before or after Wikler published his findings?

PB: I would say that it was about the same time, because I met Wikler and we discussed his work on dogs, where he showed the dissociation of the EEG from behavior and we were able to demonstrate a similar phenomenon in other species, cats, and later on, rhesus monkeys.

TB: So, you showed that some drugs would produce dissociation between behavior and EEG in the cat.

PB: That's right. The most striking dissociation was with atropine, but large doses of the drug were needed. It wasn't what you would regard as a normal dose of atropine in either animals or man, for that matter, but we noticed no untoward effects.

TB: Do you remember the research you did immediately after you got your PhD?

PB: I did some work on the effects of DFP, diisopropylfluorophosphate, an irreversible cholinesterase inhibitor. I had a student working with me then, and we became interested in a technique developed by Feldberg for injecting drugs into the ventricles of the brain. These experiments produced some interesting results but their interpretation was difficult, especially as it became apparent that the CSF-brain barrier was as potent as the blood-brain barrier.

TB: Could we review again briefly your findings on the effects of drugs? Barbiturates and amphetamines have....

PB: A direct action on the reticular formation on the brainstem, barbiturates, depressing and amphetamine, stimulating.

TB: LSD and chlorpromazine?

PB: Well, it seemed from our experiments with the measuring of thresholds for arousal to afferent auditory stimulation, compared to thresholds for arousal to direct electrical stimulation of the reticular formation, that the effects of LSD and chlorpromazine were more likely to be related to the afferent inputs, i.e., afferent collaterals, into the brainstem, this being the mechanism by which afferent stimuli produce arousal. At a meeting in Geneva in 1964, I proposed the hypothesis that chlorpromazine had an action in the brainstem, similar to that of deafferentation, and this could explain its clinical actions, but it did not arouse much interest.

TB: It was the first hypothesis about the mode of action of chlorpromazine?

PB: I think it might have been, but I'm not sure.

TB: It was an important discovery because it showed that the mode of action of chlorpromazine is different from the old sedatives. It also showed that the mode of action of LSD is different from the mode of action of anticholinergics.

PB: Yes, the hypothesis was that the anticholinergics and cholinergic agonists act more diffusely, i.e., their actions are not restricted to a particular area, which is what you would expect from the distribution of cholinergic receptors in the brain, based on studies of the distribution of the enzymes, choline acetylase and acetylcholinesterase, which showed a fairly even distribution throughout the brain.

TB: You were also one of the first to show dissociation between behavior and electrical activity in the brain after the administration of anticholinergics.

PB: We observed the phenomenon in the cat and also in primates, rhesus monkeys, whereas Wikler's observations, which I think were concurrent with ours, were in dogs. So, it seems the dissociation is not species-specific. I have to say that my friend, Vincenzo Longo, working in Rome, never agreed that the dissociation existed and I think he tried to disprove it, at the CINP Meeting in Tarragona in 1968, but I couldn't be bothered to get into a dispute, as I had then moved on to other things. I thought it was the sort of thing anybody could reproduce if they wished to.

TB: The finding about the dissociation has kept lingering on for a long time.

PB: I suppose so, because nobody has ever really examined the phenomenon in detail and we still do not know what it means. It seems strange that an organism can show sleep-like activity in the EEG while it is fully alert. You could say it shows the irrelevance of the electrocorticogram to behavior, but I don't think that's the sort of generalization we should make; but it is clear that the electrocorticogram is not always a good indicator of the behavioral state of the animal in terms of wakefulness and sleep. I believe other examples of dissociation have been found more recently.

TB: Now, let's get back to your activities after you got your PhD. Did you become involved in teaching?

PB: My first involvement in teaching was, strangely enough, in teaching neurology. The head of Pharmacology, Alistair Frazer, was of the opinion that only medically qualified staff should teach medical students. Those ideas did not last very long. There were some aspects of neurology that I did not know very well and, again, I had to learn quickly. However, I was able to give lectures on

the reticular formation and also on the EEG where I also gave demonstrations, using student volunteers as subjects.

TB: Any other important events in those years?

PB: There was the Neurochemistry Conference in Oxford in 1954, which Joel Elkes organized and I assisted with the administration. That was my first involvement in organizing meetings and the experience proved useful in later years, particularly with the early CINP meetings. It was an enjoyable experience and I met some interesting people.

TB: Can you tell us something about the Oxford meeting?

PB: It was a very mixed group, mainly biochemists, some physiologists and anatomists. I can't tell you much about the scientific aspects of the meeting as I was working behind the scenes and looking after people's problems. One of the problems I had, which interested me, thinking about it later, was that the organizers had written to invite a number of speakers from the Soviet Union but had received no response. Then, half way through the meeting, this group of Russians arrived and I had to receive them, as everyone else was busy. They had an interpreter with them, a lady, but I subsequently found that they could all speak English, so the role of the interpreter was not quite what we thought. Everybody was staying in the colleges, Magdalen College being the main one, but the Russians refused to stay in a college and we had to find them a hotel!

TB: They were probably obliged by their government to stay in hotels.

PB: I think that is true, but it all ended very amicably; they were very friendly and participated well in the meeting.

TB: Was that the first International Congress of Neurochemistry?

PB: I think it was. After the meeting it was decided to set up the International Society for Neurochemistry, and later on, there was a Journal. Brian Ansell, who subsequently joined me in Birmingham, was one of the founders. He also became Chief Editor.

TB: It was held at the time when emphasis in the transmission of impulses in the brain began to shift from electrical to chemical.

PB: Yes, the person who was most influential at the time was the physiologist Sir John Eccles, who had been a strong proponent of electrical synaptic transmission but, in a series of lectures in Oxford, described, somewhat dramatically, how he was converted to a belief in chemical transmission, i.e., that the nerve impulse crossed the synaptic junction as a result of the release of

a chemical. It was about the time that the physiologists Hodgkin and Huxley were studying transmission in peripheral nerves and the neuromuscular junction. That was a very active period but those working on peripheral nerve transmission didn't think about the brain. I have a feeling they didn't want to think about the brain because it was an extra complication.

TB: It was in those years that the presence of norepinephrine was detected in the brain.

PB: That was the work of Martha Vogt and also Von Euler. Martha Vogt published an important paper in 1953 on the levels of adrenaline and noradrenaline in the brain, showing that these substances were concentrated in the midbrain and brainstem regions, which fitted in nicely with our theories. But there were other things happening at that time. As I said, Joel went off to America in the early 1950s, and when he came back, he established this new department of Experimental Psychiatry; and when I was appointed to a Lectureship in Electrophysiology, I joined him in the new department.

TB: It was the first department of experimental psychiatry in the world.

PB: Probably so. Sometime later, I was offered a Fellowship by the Rockefeller Foundation of New York and I was told I could choose where to go to study. The options then were the Department of Anatomy at UCLA with Magoun or the Institute of Physiology at the University of Pisa with Morruzzi.

TB: And you chose Pisa.

PB: It was a difficult choice, but in the end, I went to Pisa because they had developed a technique for recording the activity of single neurons using microelectrodes. My feeling was that analyzing EEG's was probably not going to get us very far, and that further advances were likely to be made by studying the activity of single neurons in the brain, how their activity was affected by drugs.

TB: Before continuing with your experiences in Pisa could you tell us something about the Department of Experimental Psychiatry. Where did the support come from?

PB: There was support from a number of places and there seemed to be a lot of money available. The main source that I was familiar with was the Rockefeller Foundation which provided my Fellowship. There was the government money from the Ministry of Health and there was a mental health research organization, which was subsequently taken over by the Medical Research Council. But all these were grants, i.e., for a limited period. I was not aware of any funding from pharmaceutical industries at that time.

TB: Was it an independent department?

PB: Yes, it was an independent department of the University.

TB: Who were the people in the department?

PB: Joel's wife, of course, Charmian, and there was a psychiatrist, Felix Letemandia. There was also a psychologist, Tony Harris and an experimental psychologist, Malcolm Piercey. In addition, there was a biochemist, John Crammer.

TB: How many people were in the department, about half a dozen?

PB: Probably more. In the basic research section there was a biochemist, named Archie Todrick and a pharmacologist, Heinz Ginzl. There were also people on short-term contracts.

TB: Wasn't Mayer-Gross also a member of the team?

PB: Mayer-Gross had worked at the Creighton Royal Hospital, in Dumfries, Scotland. He had already retired when Joel consulted him about recruiting a fairly senior person to take charge of the clinical work of the department. I was told that when Joel asked Mayer-Gross whom he would recommend, Mayer-Gross said, "What about me"?

TB: Can you tell us something about Mayer-Gross?

PB: I understood that he had been the Professor of Psychiatry at Heidelberg University in Germany and had left in the 1930s for Scotland. I believe he was one of the co-authors of a *Textbook of Psychiatry*, but I didn't see a lot of him in Birmingham.

TB: You had some interactions with him, did you?

PB: Yes. That was when I returned from Italy in September 1957. Joel had already left and things were pretty chaotic as there was no one in charge. Mayer-Gross and I did not see eye-to-eye; he did not approve of what I was doing.

TB: But, he was on the team.

PB: Yes, he was one of the team.

TB: There was also Brian Key.

PB: He was one of my Ph.D. students. He did most of the experiments on measuring thresholds and we published that work in the EEG Journal and the British Journal of Pharmacology.

TB: Was he your first Ph.D. student?

PB: No, my first Ph.D. student was a man named Jim Hance. He was a zoologist as was Key. They were both Birmingham graduates; in fact, the then Professor of Zoology, Otto Lowenstein

was very helpful in finding students for me. Hance did the experiments with intraventricular cannulae, injecting drugs into the cerebral ventricles and observing the effects on the EEG and behavior. This was the work for his Ph.D. After I came back from Pisa, I attended a meeting in Brussels. Magoun was there and he invited me to work in his laboratory but, as I'd just had a year off and things in Birmingham were a little difficult, to say the least, I had to decline. But, I think, I ended by saying, there was someone else from my laboratory who could be interested. So, Hance went in my place and stayed. He worked with the Killams and moved to Stanford with them and then on to Davis. I visited him and his wife Ann in Los Angeles, and later on, he helped me to find a house to rent on the Stanford campus. Then they moved to Davis and I saw him again when I visited the Killams. After that I am afraid we lost touch.

TB: Actually, Keith Killam died. Eva Killam is still around. I saw her at the last ACNP meeting.

PB: Oh, dear. I did not know about Keith. I last saw them both at the Pharmacology Congress in London when we had dinner together.

TB: Where was the Experimental Psychiatry department located?

PB: The department was housed in the University of Birmingham Medical School. The Medical School and the general hospital, the Queen Elizabeth Hospital, were on the same site. Most of the clinical work of the department went on at the mental hospital, All Saints, which was some distance away, and that is where I used to go to do EEG recordings on patients. There were psychiatrists at the Queen Elizabeth Hospital but I don't think there was a department, i.e., a University Department of Psychiatry.

TB: And, the director was Joel. I read somewhere that at the time, there was no other Professor of Psychiatry in Birmingham.

PB: That's right. There was no Professor of Psychiatry, but there was certainly a Professor of Neurology, Philip Cloake, whom I knew very well. However, there were two psychiatrists in the hospital who I think were consultants. I was with them once at a meeting and, after giving my paper, one of them said that it didn't matter how a drug worked as long as it had an effect on the patient. I think it was their attitude that was one of the reasons for Joel deciding to leave. I don't know what he would say about this, but certainly it wasn't lack of financial support. There were other psychiatrists in Birmingham who were more supportive. There was a day hospital in Moseley, Uffculme Clinic, which was an outpost of All Saints Hospital where the medical

superintendent, Dr. O'Reilly was very helpful and provided Joel with facilities for clinical trials. I believe the MRC Unit would, at least partially, have been established at Uffculme Clinic.

TB: Do you remember the visit of Ernst Rothlin?

PB: I remember it very well. Rothlin was Professor of Pharmacology at the University of Basel and Director of Research at Sandoz, where LSD had been discovered by Albert Hoffman. Rothlin gave a lecture on LSD which I found quite fascinating, although not much was known about its pharmacology at the time. Also, Rothlin had brought us a sample of LSD and, perhaps rather foolishly, we did experiments on a group of about 12 normal volunteers, including ourselves and other members of staff of the Medical School and All Saints Hospital. The experiments were supervised by Joel's wife, Charmian, and I did the EEG's; we recorded everything we could think of, including things like manual dexterity and reactions to various images. The results weren't very striking, but were, I suppose, pioneering, because it was the first experiment in normal subjects, apart from those of Hoffman and Stoll. There were changes in perception, but the EEG changes were relatively slight, in the direction of increased alertness. The drug appeared to exaggerate underlying personality traits in the subjects, so that people who were slightly obsessive became more so and subjects who were slightly paranoid showed increased symptoms. Personally, I think it was a mistake to use colleagues and friends as subjects in these experiments. Perhaps medical student volunteers might have been preferable, although this could have had its dangers, as some years later, I was approached by a medical student who said he understood we were studying LSD and he could supply some! I thanked him and said "No," as by then, possession of the drug was illegal and I had the only legitimate supply.

TB: What about depression? Did you encounter depression in any of the subjects?

PB: No, but we did encounter some severe reactions. There was one colleague who did not seem to be responding to a dose of 25 micrograms. Joel came in and Charmian asked if we should give him some more, but Joel said "No." So we waited and soon after he got a very strong reaction, which I think went on for two days. People who were still showing the effects of LSD after the experiment had finished, were given a small dose of a sedative, usually chlorpromazine. However, this particular subject's wife was a doctor, and she said, "Nobody is going to treat my husband," so she refused him the sedative and the effects of LSD persisted for two days. So, these were interesting times.

TB: Could you tell us something about Rothlin?

PB: Ernst Rothlin was a very nice man and I got on quite well with him. During his visit, we discussed the idea of a new international organization devoted to Neuropharmacology and both Joel and I said that we would be enthusiastic supporters. Rothlin said he would discuss the proposal elsewhere and let us know the results.

TB: You were instrumental in opening up the field of Neuropharmacology?

PB: Somebody referred to me once as the “Father of Neuropharmacology,” but I do not think that’s true and it was probably just a joke.

TB: You pioneered with your research in neuropharmacology, using microelectrode techniques.

PB: Yes, but I still thought of neuropharmacology as a branch of pharmacology.

TB: Still, you were one of those who opened development in neuropsychopharmacological research.

PB: Yes, that is probably true, and I think I held the first formal appointment as a Neuropharmacologist, in 1958, and that was the year in which I was awarded my D.Sc., which was for studies in the field of Neuropharmacology. I did think it was unnecessary to have both, psycho- and neuro- in the name of CINP, the new organization, because what is psycho- if it isn’t also neuro-? However, I believe some people, e.g., psychologists would prefer to have both in the name.

TB: What would you have preferred?

PB: Just Neuropharmacology, but, then, others would prefer just Psychopharmacology and I am a Founder Member of the British Association of Psychopharmacology. I think the combination, Neuropsychopharmacology is a bit cumbersome, that’s all, but we all have to compromise.

TB: I think it was during Rothlin’s visit to Birmingham that the idea of having an organization in neuropsychopharmacology was first discussed.

PB: It was, and I believe Joel pursued the idea further and talked to other people. In fact, Rothlin might have asked him to do so. A lot of people seem to have suggested that it was their idea.

TB: Am I correct that the night before you went to Pisa, Joel told you that he might be leaving, right?

PB: Yes, that’s true. How do you know this?

TB: I learned it from one of yours or his publications.

PB: It wouldn't have been in any of my papers. He'd been back in Birmingham for some years but was still visiting Washington frequently, and it was the night before I was due to leave for Pisa that we had dinner together at the Cafe Royal in London, and that's when he broke the news and he said that he hoped I might eventually join him. I had been attending a meeting at the Institute of Psychiatry at the Maudsley Hospital and Denis Hill, who was in charge of the EEG Department there, offered me a job. I was in turmoil and didn't know what to do. I thought the department in Birmingham might break up. Anyway, I turned down the job at the Maudsley as I knew that it wasn't a very happy place. I knew Sir Aubrey Lewis quite well, as I had been advising him on setting up a new laboratory for electrophysiological research. There had been occasions when I was lunching with Aubrey Lewis in the refectory and other people whom I knew would come in but would not join us. It seems petty but I did not think there was a very good atmosphere at the Maudsley Hospital, so I turned down the job and went to Pisa and continued with my research. I subsequently had my opinion of the atmosphere at the Maudsley confirmed by others.

TB: When did you go to Pisa?

PB: It was in 1956. I went by train on a first class sleeper from Paris and it was a pleasant journey. I had taken a good supply of drugs with me and was a bit worried about going through Customs. It was fortunate that I did take them, as there was nothing at the Institute of Physiology in Pisa. My purpose in going there was to learn, and to use the technique of the floating microelectrode, with which they were recording the activity of single cells in the brain. I thought it would be very complicated, but it was not. Essentially it consisted of a piece of fine enameled wire, pushed gently into the brain until the activity of a single neuron was picked up. The other end of the wire was clamped but a loop was formed so that the recording tip was floating and would move with movements of the brain. I learned this technique very quickly and I worked with an Italian, Dr A. Mollica, who was Moruzzi's first assistant. We worked hard, including on Saturdays, which was the system in Italy and we obtained some very interesting results which were published in Moruzzi's journal, the *Archives of Italian Biology* (Arch. Ital. Biol.). I believe that it was the first time that such experiments had been performed. However, we were injecting the drugs intravenously and since there were changes in blood pressure when the drugs were injected, we could not decide whether the effects observed were due to an action of the drug on the neuron we were recording, or some indirect effect via a change in blood pressure. I realized that this technique

wasn't going to get us very far and began to think about alternatives. Nevertheless, I persevered with my year in Pisa, and enjoyed the Italian sunshine and the culture. Two events occurred during my stay in Pisa, both of which were important to me. The first was an invitation to attend and present a paper at a Symposium "The Reticular Formation of the Brain" at the Henry Ford Hospital in Detroit in March 1957. It was a great experience and my presentation was well received. There were only two other participants from the UK, Geoffrey Harris from London and the neurosurgeon, Sir Geoffrey Jefferson, both of whom I got to know well. It was also an opportunity to visit other centers in the US, including that of Harold Himwich at Galesburg, and Magoun's laboratory in Los Angeles. I also visited Washington where I was offered a post in Joel's laboratory at St. Elizabeth's Hospital. The second event was an invitation to attend and present a paper at a meeting on "Psychotropic Drugs" to be held in Milan in May 1957.

TB: Could you tell us something about that meeting?

PB: The meeting was sponsored by the Institute of Pharmacology in Milan, the head of which was Professor E. Trabucchi. But Trabucchi was a retiring kind of person and liked to remain in the background, so the meeting was organized by Silvio Garattini, whom I already knew, and V. Ghetti.

TB: Later on, Silvio published the proceedings of that symposium with Ghetti.

PB: I had my first wife and two children with me in Pisa, and we all went to Milan and stayed in a very nice hotel. There was also a visit to La Scala, where I heard the tenor, Guiseppi de Stefano for the first time. Scientifically the meeting was a great success and an opportunity to meet other people working the same or related fields. During the meeting, I received an invitation from Rothlin to attend an informal meeting to discuss the proposed organization on Neuropharmacology.

TB: How many people participated?

PB: I think about a dozen.

TB: Can you remember the people who were present?

PB: Rothlin, Radouco-Thomas, de Boor, Denber, and others whom I can't remember.

TB: In the records of the CINP history committee, both Corneille Radouco-Thomas and Wolfgang de Boor independently suggested to Trabucchi prior to that meeting to propose the founding of an international society in Neuropsychopharmacology.

PB: I don't think that's true, but I am not sure. Trabucchi was a very modest, retiring man. I think he liked to facilitate things and gave his support to the meeting, but I am not sure if he proposed it. Personally, I do not think it is important who had the original idea. We all have ideas from time to time and do not pursue them, and then someone else takes them up. As far as I am concerned, I first heard mention of an organization which eventually became the CINP, in Birmingham in 1954 or 55 during Rothlin's visit, not in Milan in 1957.

TB: The question is whether it was Trabucchi or Rothlin who initiated that meeting during the Milan symposium, and whether it was Trabucchi or Rothlin who chaired it?

PB: As far as I know, it was Rothlin, and it was certainly Rothlin who chaired it.

TB: Do you remember anyone else who participated? I think Hans Hippus was there. PB: He might have been there, although he was not a participant in the Symposium. But I know Rothlin chaired the meeting that led to the founding of the CINP.

TB: What about Deniker?

PB: Deniker was there and also Denber and I think Bente. We had quite a long discussion, but the decision to found the CINP was deferred in Milan until the Second Congress of Psychiatry in Zurich, which was to take place in September 1957. In my opinion, this was not a good idea because most of the people who would become members of the organization were already in Milan and, apart from psychiatrists, very few were likely to attend the meeting in Zurich. However, Rothlin maintained that as pharmacology would be included in the title, it would be wise to consult the International Union of Pharmacology (IUPHAR) and get their approval; it would be a bad move to go ahead without their agreement, and he was probably right. There was also discussion about a Journal, which turned out to be *Psychopharmacologia*. It appeared that Rothlin had been in discussions with a publisher but did not disclose very much information.

TB: Now, the story goes that in Milan there was also another important luncheon meeting relevant to the founding of the CINP in which you participated. Do you remember?

PB: I remember the meeting and that we had lunch, I think at Trabucchi's department, as I remember talking to him, but precisely what it was about I can't remember. I should think it was probably a preparation for the meeting in Zurich but cannot be sure.

TB: Were you involved in the preparation of the inaugural meeting in Zurich?

PB: No, I had other problems at the time. I had received a message that Joel Elkes had already left Birmingham, so I returned from Pisa a month early, in August to find out what was happening. Things were pretty chaotic and the finances of the department were in a mess. Then the University appointed me Acting Head of the Department and the Vice-Chancellor, Sir Robert Aitken, said to me, "This is your opportunity." In retrospect, I have sometimes wondered if Mayer-Gross had expected to take over from Joel. I was probably lacking in experience and not very good at handling other people. The main problem was that the three staff members, Joel had recently recruited, Letemendia, Harris, and Crammer, who were all medically qualified, were on short-term contracts, and the money was running out. I was told by the Rockefeller Foundation that they would not be renewing their grant, and I knew that the people at the MR were not very happy, as they had set up a Research Unit with Joel as director and with some staff appointed, and he then abandoned it at very short notice. Not many people knew about this, but I saw it written on a headed notepaper about the Unit. Mayer-Gross accused me of getting rid of good people and of destroying what Joel had built up, but I really had no choice as the finances were in a mess. I probably did not handle Mayer-Gross very well. He was a nice man, but a very dominating character and, of course, famous, whereas I was very much at the beginning of my career. There was one other factor which I considered important, and that was that as I did not have a medical qualification; I did not feel that I could be responsible for the work of medically qualified staff. Perhaps Mayer-Gross and I ought to have found a way of working together but it would have been very difficult. I think it was probably a mistake for him to come to Birmingham after he had retired. Another important event which occurred that year was that I was invited to meet Sir Harold Himsworth, the Secretary of the MRC in London. We had an interesting discussion as a result of which I was asked to present my research findings and future plans to the MRC's Clinical Research Board. I know that discussions went on behind the scenes with the Vice-Chancellor, and the MRC decided to establish a research unit in Birmingham, The Neuropharmacology Research Unit, with myself as Honorary Director. This was my first official appointment as a neuropharmacologist. Eventually, the university appointed a Professor of Psychiatry.

TB: Who did they appoint?

PB: Professor William Trethowan who came from Australia. It was clear that there could not be two departments of psychiatry and I was quite happy to change the name of mine. I would have

preferred Neuropharmacology, but the then Professor of Pharmacology, Alistair Frazer, would not accept that so, as a compromise, we became Experimental Neuropharmacology. I must say that Trethowan and I got on extremely well, and he was very supportive of our research.

TB: But in spite of all the problems you had at home, you went to Zurich to attend the inaugural meeting of the CINP.

PB: Yes, I went to Zurich for the 2nd World Congress of Psychiatry. I felt that as I had been involved in neuropharmacology from the beginning, I should be there.

TB: That meeting in Zurich was organized by Rothlin and was by invitation to a dinner.

PB: The dinner was in the first class restaurant at the Zurich railway station.

TB: Insofar as we know there were 33 people at that dinner, right?

PB: I think so. From the UK, apart from myself, there was Michael Shepherd, Sir Aubrey Lewis, and Derek Richter. Humphrey Osmond was also there.

TB: What about Linford Rees?

PB: I don't think he was there, but I cannot be sure.

TB: Some people say he was, but some other people say, he wasn't. It was a very distinguished group.

PB: Probably. A lot of people felt motivated to make speeches. At the end, there was a formal proposal from Rothlin, that the CINP should be founded and this was agreed unanimously as far as I can recall. Rothlin became its first president and various people were proposed for the committee.

TB: You and Deniker became the first councilors.

PB: Yes. I was proposed by Aubrey Lewis. I think that Rothlin wanted another pharmacologist on the committee, which seemed sensible. Also, he probably wanted a representative from the UK.

TB: Another version is that it was Denber's suggestion that you and Deniker became councilors because of your contributions to the then new field.

PB: It is possible that Denber supported my nomination, but I know it was Aubrey Lewis who proposed me as he was sitting next to me. Anyway, the CINP was established and I was a member of the Council. Our immediate task was to organize the first meeting in Rome in 1958, which was in 12 months' time. I thought it was crazy, but we did it!

TB: What was your role in organizing that congress?

PB: I was asked to organize one of the symposia. It was the first Symposium, "Methods and Analysis of Drug-induced Behavior in Animals." As I was also the first speaker, it was chaired by Rothlin and Jules Masserman.

TB: Could you tell us who were involved in organizing the congress? Was Rothlin involved?

PB: Both Rothlin and Trabucchi were involved. I think Trabucchi made most of the local arrangements, as Chairman of the Local Organizing Committee, whereas the program was the responsibility of the Executive Committee, chaired by Rothlin.

TB: In addition to Rothlin and Deniker, could you tell us who the others were on CINP's first executive? There were two secretaries.....

PB: Yes, there were two secretaries, Radouco-Thomas and Denber.

TB: And the treasurer was Stoll.

PB: That's right. It seemed that it was dominated by Europeans.

TB: Could you tell us something about the Rome congress?

PB: I think it was a very successful meeting. We tried to put together a program which covered all the different scientific disciplines contributing to Neuro-Psychopharmacology and I think we succeeded. Certainly, a number of people who had attended, told me later how successful they thought it was. There was an excellent social program as well, although I was obliged to miss the audience with the Pope, as I needed to prepare my talk. Apart from the opening symposium in which I participated, I persuaded my colleague, Brian Ansell, who had just joined me in Birmingham as Lecturer in Neurochemistry to give a lecture on "The Present State of Neurochemistry."

TB: Didn't you edit the proceedings?

PB: The Executive Committee met on the last day of the meeting and decided that the proceedings should be published. I, Deniker, and Radouco-Thomas were appointed as editors. We had a difficult task as many people were already leaving and had not been asked to prepare a manuscript, and there was no publisher. However, we succeeded, and the Elsevier Publishing Company proved to be very cooperative. I think Radouco-Thomas had already been in touch with them. Inevitably some contributions were missing as we could not delay publication for too long. I think that the book was well received. This was my first venture into publishing, and it prepared me for the future.

TB: How many people attended the congress?

PB: There were more than 500. I think some people came because this was something new. There weren't many people from the UK at the inaugural meeting in Zurich and my impression was that the bulk of the psychiatric population in the UK wasn't terribly interested. However, when they heard about the success of the Congress in Rome, many more became interested, and eventually became members of the CINP.

TB: Could you tell us something about your research after you returned from Pisa?

PB: It was some time before I could get back into experimental work. As I was in charge of a department that had been abandoned by its previous head, I had a great deal of administration to contend with and was lacking in experience. There was also a good deal of planning to do. Fortunately, research funds had not dried up completely, in spite of the Rockefeller Foundation not renewing its grant. I think that was a personal grant to Joel anyway. I still had my funding from the US Air Force, which was generous, and the University provided a number of new appointments, including a Lectureship to which Brian Ansell was appointed, as I have previously mentioned. And, eventually, the MRC established its Neuropharmacology Research Unit under my direction, occupying accommodation provided by the University. During my absence in Italy, the electrophysiological research had been kept going by two postgraduate students who kept in touch with me by mail. Now I had a new student working with me, making microelectrode recordings of single neurons in the brain. I had heard about iontophoresis being used by some people at University College, London and I visited them. A similar technique was being used at John Eccles' laboratory in Canberra.

Then, at a meeting of the Physiological Society, I met John Wolstencroft who was working in Leeds at the time. He was planning a visit to Morruzzi's laboratory in Pisa and wanted my advice. Our discussions led to the discovery of many mutual scientific interests, and we both concluded that the use of microiontophoresis to apply active substances onto single neurons in the brain, whilst recording their activity, was the way forward for both of us. I was able to persuade the MRC to create a senior appointment for John in the unit and he moved to Birmingham. This was the beginning of a very exciting time for both of us. The equipment we were using at the time was very primitive and the experiments very time-consuming. Because of electrical interference in the Medical School during the day, although we were using a Faraday Cage, we had to work at

night when the lifts could be switched off. Also the only way we could record the action potentials was by photographing onto 35 mm film. Then, after the film was developed, one of us would take it home and count the activity usually over a 10 second period. Eventually, we designed and had made electronic equipment for recording and counting the neuronal activity that provided a printed output of the rate. The people working with iontophoresis in London and Canberra were studying neurons in the spinal cord and, as far as we knew, no one had used the technique in the brain. We obtained some exciting results. Using putative transmitters, such as acetylcholine, noradrenaline, and serotonin, we were able to classify the brainstem neurons into different types according to their responses. Thus, when acetylcholine was applied, some neurons showed a pattern of excitation whilst others were inhibited, and a third group was unaffected. A similar pattern of activity was shown by the other two substances, noradrenaline and serotonin. Furthermore, some neurons responded to just one substance, some to two and, rarely, some to all three, and the pattern of responses could be a mixture of excitation and inhibition. From this complex pattern of responses, we attempted to classify neurons in the brainstem and, although this classification was somewhat crude, it was a beginning. We then started looking at interactions with centrally acting drugs, for example chlorpromazine, LSD, and amphetamine. One interesting finding was that LSD antagonized the actions of serotonin (5-HT) which supported the hypothesis put forward by Gaddum, in 1956, based on studies on peripheral nerves. At the time, some workers in the Physiology Department in Birmingham had isolated a substance with oxytocic properties, which was released from the cerebral cortex in response to stimulation of peripheral nerves. John Wolstencroft was very excited about this and wanted us to test it in our experiments. I was not keen as we knew nothing about the chemistry of the substance, only that it was oxytocic. Nevertheless, we did some experiments and found that the substance had some activity on brain stem neurons but the results were difficult to interpret. Later on, the substance we were using was shown to be a prostaglandin, which has an important role in platelet aggregation. We also did some experiments with a "sleep-inducing" substance, discovered by Monnier working at the University of Basel in Switzerland. He sent us samples by air and we collected them at the airport and rushed them to the lab. Again very little activity was found, and I was not very pleased when I discovered that Monnier was sending us placebos as well, without telling us which was the active sample and which was not.

TB: You said, if I understood it correctly, that you were involved in classifying neurons according to their response to neurotransmitters, and if I remember well, you also studied interactions between neurotransmitters and drugs by using iontophoresis. Could you give us an idea what you actually did?

PB: We used multi-barreled microelectrodes which consisted of fine glass tubing, drawn out to a fine tip. We invented a device in which the glass tubing was held vertically and a weight attached to the bottom end. In the center was a circular electrical heating element. When the current was switched on, the tubing was heated and the weight pulled it down so pulling out the glass to a very fine diameter. By adjusting the weight and current, we were able to achieve the size of tip we needed, usually 5 microns diameter. With this size, we were able to isolate single neurons in the brainstem. A number of these tubes would be glued together, usually five, but I have heard of people using electrodes with up to eight barrels. The central barrel was filled with saline solution and used for recording the activity of the neuron and the other barrels around it were filled with aqueous solutions of the substances we wished to test. Clearly only substances that ionized in solution could be used in this way, and we were lucky that most of the substances we were interested in did ionize. By passing a very small electric current through the relevant barrel, the substance under test was released close to the neuron being recorded. Usually one of the barrels of the electrode was filled with saline as a current control, i.e., to test the effect of the current alone on the activity of the neuron. We assumed that the amount of substance released from the tip of the electrode would be dependent on the strength of current passed. Sometime later, one of my colleagues did some tests using radio-labeled compounds to measure the quantity released with different current strengths and confirmed that our assumption was correct. We seemed to be developing a new area of CNS research and I thought it might be interesting to make it known to a wider audience. Since I was a member of the organizing committee for the 3rd CINP Congress to be held in Munich, I proposed that there should be a session on studies on single neurons and this was accepted. John and I put together a program to include those who were working in similar or related fields; these included Salmoiraghi, who was working at Joel's new unit in Washington, and Krnjevic, who had worked with Eccles and was then in Cambridge. The session was held in a fairly small auditorium, which we thought would be adequate, but we were completely wrong as

we had people queuing at the door to get in and others listening from the corridor outside. I was pleased with the reception we received.

TB: Weren't there some problems in the CINP in those years?

PB: I am afraid there were. Rothlin was not an impartial chairman. He would lead the discussion and expect other people to agree with him. When a topic came up for discussion, there was no way in which members of the committee could put their own views before a conclusion was reached. I think it was Denber, one of the secretaries, who objected rather vociferously, and I felt obliged to support him, although I had some sympathy for Rothlin, as I knew him personally, having visited him at home and at his retreat on the top of the Rigi. I thought then that he did not know any other way to behave in such circumstances, and I realized that the universities in Switzerland must have been run on very autocratic lines, as were those in the UK at one time.

TB: What was it about Rothlin's actions that created the problem?

PB: Well, it was really about the way decisions were made, because Rothlin wanted to have his way in everything, and it was impossible to get him to listen to reason.

TB: Was there any real issue?

PB: I don't think so, but maybe you should talk about that to other people who were there. Have you talked to Denber?

TB: He died.

PB: Did he? Oh, I didn't know. I'm sorry to hear that.

TB: I talked to him about it some time ago, but he didn't say very much.

PB: No, he wouldn't have. He would probably sit on the fence for diplomacy's sake.

TB: Am I correct then that you supported Denber?

PB: I did, because I felt it was necessary; although I appreciated that Rothlin was doing what he did because it was the only way he knew and one couldn't change that.

TB: Some people told us that it was about finances.

PB: I don't know if that is true. However, I felt that Denber had a point. Then, Seymour Kety joined us and told us to pull together, which we did.

TB: I understood from some people that it was a rather difficult situation.

PB: It seemed that the CINP might collapse, and it was probably saved by the intervention of Seymour Kety.

TB: Some of the founders, Denber and Radouco-Thomas, resigned.

PB: Yes, they resigned, but my memory isn't terribly good on this, because one tries to forget unpleasant things.

TB: The important thing is that the CINP survived and by the time of the 3rd congress everything was fine.

PB: Yes it was.

TB: The fourth CINP meeting was in Birmingham. Wasn't it?

PB: Yes, it was the meeting I hosted.

TB: It was a great meeting.

PB: Was it? Good.

TB: Yes; it was the first meeting I attended.

PB: At the end of the week, we went to a performance of Henry V in Stratford, and I fell asleep during the battle scene! So, it must have been pretty exhausting.

TB: It had an excellent program. It was also interesting in terms of organization. Everyone stayed on campus in the student halls of residence.

PB: Oh yes, but we hadn't much alternative. There wouldn't have been enough hotel accommodation in Birmingham at that time. There probably is now. I thought it was a disaster, at the time, because people were in rooms without wash basins. The student accommodation then was quite Spartan. It has been improved considerably since.

TB: There was one bathroom for about ten rooms.

PB: That's right, yes, not ideal for people who were used to better things. However, I think that the meeting was fairly successful, scientifically.

TB: I remember that Max Fink delivered one of the plenary lectures on clinical neurophysiology, on the new science, pharmaco-EEG.

PB: Yes he did, and it was well received.

TB: Yes, I think so. And there was also a lecture by the president.....

PB: That was the Austrian, Hoff.

TB: Can you tell us something about the budget and finances of the Birmingham meeting?

PB: I believe we covered our costs. I don't think the University was quite as helpful as it should have been, although we were provided with all the accommodation we needed, including a large

lecture theatre for the plenary sessions. We had adequate financial support, some from the United States, and most of the pharmaceutical companies I contacted gave us generous support.

TB: So, the meeting didn't cost CINP any money?

PB: Not as far as I am aware. I don't think the CINP had much money at the time. There was a bank account in Basel, and the subscriptions were going in there, but there did not seem to be much money available.

TB: So, there was no money from the CINP.

PB: No. I think the meetings at that time were supposed to be self-supporting. We were able to cover our expenses and pay the expenses of the speakers, but there were no large grants. TB: Is there anything else you would like to say in relation to the Birmingham meeting? PB: During the meeting, there was discussion at the Executive Committee as to who the next president might be. I thought it was time we had someone from the UK, and suggested Sir John Gaddum, who was Professor of Pharmacology at Edinburgh at the time and was well known internationally. Unfortunately, when I approached him, he was obliged to decline the invitation as he had developed esophageal cancer. It was in that year, also, that I had been nominated for a professorial chair. Prior to that, I had been appointed to a Readership, which was the most senior non-professorial appointment in the University and was usually awarded for distinction in one's research field. However, the Vice-Chancellor said to me, "It's time we gave you a Chair." The appointment should have been made in October, but he pushed it forward, so that I had professorial status in time for the meeting.

TB: Before that you were Acting Head.

PB: Yes, I was. They had made me Acting Head of Department, but without a Chair. I think that at the time, I was the only non-medical head of a department in the Faculty of Medicine, but that did not seem to matter and I got on well with my colleagues.

TB: It was after the Birmingham meeting that you became treasurer of CINP.

PB: Yes, I think it must have been then that I became Treasurer. I had served for six years as Councilor and thought it was time for new faces on the Committee, but they must have invited me to become treasurer and I accepted.

TB: And you continued to be treasurer for 6 years.

PB: Was it as long as that?

TB: I think it was.

PB: I can remember at the Washington meeting having to go to the bank to draw out a large sum of money in cash in order to pay the speakers' expenses. Why we had to do it in that way I don't know and I was concerned at having to travel across Washington in a taxi with such a large amount of cash. Perhaps I should have had an escort! I then made the payments from my room in the hotel.

I think it was the Sheraton, wasn't it? TB: Yes, it was at the Sheraton.

PB: Max Fink and I were invited by the Program Committee to organize a Symposium at the Washington meeting.

TB: What was the symposium on?

PB: The topic was "Anticholinergic Drugs."

TB: Yes.

PB: I still had an interest in that area at the time.

TB: Would you like to say something about your symposium?

PB: I think it was successful. It was certainly well attended; we invited a number of distinguished speakers, including Wikler, Votava, Herz, Longo, Domino, and Jacobsen.

TB: In those years, there was still interest in publishing the proceedings of meetings.

PB: At that time, I had been involved in editing the proceedings of a number of CINP meetings. I had formed a good relationship with the Elsevier Publishing Company, who had a series of books, called "Progress in Brain Research," which later became a journal. They proposed to Fink and me that our proceeding should be one of these volumes.

TB: I think you were involved in editing the proceedings of the 1st, 3rd, 4th and 5th congresses.

PB: Yes I was, but with different collaborators each time. I should have stopped, but I enjoyed doing it.

TB: You co-edited the Washington proceedings with Brill, Cole, Deniker, and Hippus.

PB: That's right, and that was quite a big volume, wasn't it?

TB: Yes.

PB: They were getting too big, I think.

TB: Yes.

PB: Well, you know, I have enjoyed all the CINP meetings I have attended.

TB: By the time of the Washington congress, in 1966, you were also involved with Mimmo Costa editing a journal in the field.

PB: It happened in the early 1960s, at a meeting in Milan on “Adrenergic Mechanisms,” held at the Mario Negri Institute, where Silvio Garattini was director, that Costa asked me if I would be interested in co-editing a journal with him. Before that, Elsevier, who had published all the CINI Proceedings up to then, told me that they would be willing to publish a CINI Journal, taking all responsibility, including financial. This would have meant publishing the proceedings of meetings in the journal rather than as books, which were getting rather large. However, when I put the proposal to the CINI Executive Committee, it was rejected. This made me rather more sympathetic to Costa’s approach. It is interesting that the CINI did, later on, start a journal and I think, it has proved successful.

TB: What was the name of Costa's journal?

PB: It was the *International Journal of Neuropharmacology*, which had been founded a few years earlier by Radouco-Thomas and Brodie. I knew about it as Radouco-Thomas had discussed the proposal to found a journal with me. I was already a member of the Editorial Board. Later on, Costa and I thought it would be better to simplify the title, so we changed it to *Neuropharmacology*, which it still is.

TB: And you have been editor of that journal since . . .

PB: No, only until 1993.

TB: So, until about 10 years ago.

PB: Yes, I retired from my university post in 1986, and I thought editing was something I could do in retirement. Also, Costa wanted to give up at that time, so, for a while, I was sole editor. Costa and I had hoped to appoint, or at least recommend, our successors as editors, but that was not to be. The journal was published by Pergamon Press, which was owned and run by Robert Maxwell, with whom I had always got on well. He had stated that he would never sell Pergamon Press, as it was one of his earliest ventures. However, when he ran into financial difficulties shortly before his death, he did sell up, and the new publisher had new ideas and wanted to appoint their own choice of editors. So, I resigned. I think it was time to do so, although I had enjoyed doing it.

TB: So, you kept the journal, but you gave up your CINI activities by the ‘70s.

PB: I think that is correct. The number of meetings I was attending was getting too many and that is why I dropped out of the CINI. I used to enjoy the meetings, but I had to think about where I wanted to present my work, particularly as I was working on single cells. I was also getting

involved with the British Psychopharmacological Society and the International Union of Pharmacology.

TB: When was the British Psychopharmacological Society founded?

PB: It was in the early 1970s.

TB: Aren't you one of the founders?

PB: Yes, I was, but it was a difficult birth.

TB: Why?

PB: Some of us in the UK had been discussing the possibility of establishing a British Psychopharmacology group along the lines of the ACNP. People such as Roger Brimblecombe, Hannah Steinberg, and others, were encouraging me to start something, but at the time, I had too many commitments elsewhere. Then a letter appeared in the Lancet which proposed much the same thing, except that it was clear that it would include only people who were doing clinical work. I then had no choice but to get involved. There was a meeting at the Royal College of Medicine in London, where there was a somewhat heated discussion. Eventually it was accepted that there were people working in basic sciences, i.e., biochemistry, psychology, and pharmacology, which were making a significant contribution to psychopharmacology. Our opponents seemed to think that psychopharmacology should be purely clinical. The most difficult person was Max Hamilton, who was Professor of Psychiatry at Leeds. He and I had a big bust up during the CINP meeting in Paris in 1974. But eventually, we won the day and the BAP was founded along the lines of the CINP, with an equal balance between clinical and nonclinical members and alternating chairmanships.

TB: So the difficulties were resolved and the Association was founded.

PB: Yes.

TB: And, some years later, you became President.

PB: Hamilton, of course, became the first President. That was inevitable. Then he was followed by Coppen, although it should have been a scientist, and I became President in 1978.

TB: Could we shift back to your research after the 1950s?

PB: As I have already indicated, I was becoming less interested in behavior and more interested in what was happening at the single cell level in the brain. I felt that I could leave behavioral

studies to other people. So, I recruited a psychologist, Ian Stolerman to my department and he did psychopharmacological experiments with animals.

TB: When did you do your work on opioid receptors? Wasn't it in the late '70s?

PB: No, it was earlier than that. I had another sabbatical, when I was offered a one-year Fellowship at the "Center for Advanced Studies in the Behavioral Sciences," which was located on the campus of Stanford University in California.

TB: When was that?

PB: It was in 1967. It may seem strange since, at that time, I was relinquishing some of my interests in behavioral studies. Still, it seemed to be an opportunity not to be missed.

TB: And what did you do in Stanford?

PB: It was a "Think Tank," where people went mainly to think and write. There were no laboratory facilities, but I could probably have arranged to work in the Department of Pharmacology at Stanford Medical Center, as I knew a number of people there, including the Killams. I decided to spend my time writing, which was what most Fellows at the Center were doing. And, of course I received many invitations to visit other laboratories and to give talks. I had been asked to write a chapter on "The Phenothiazines" for a book which I think was the "Annual Review of Pharmacology." I spent some time on that as I decided to make it as comprehensive as possible; I covered the history, chemistry, pharmacology, and clinical uses. I was told later that my chapter has been found useful for teaching! I also wrote another chapter for a book, whilst I was at Stanford, as well as starting to plan a book of my own.

TB: After your return to Birmingham from Stanford, I suppose you were mainly involved with your research.

PB: I had hoped to be, but again, it was a difficult time. Having left my department in the hands of my colleague, Brian Ansell, for a year, with the MRC Unit being looked after by John Wolstencroft, there were many administrative matters to deal with. There was also the journal which a friend and colleague, Ted Marley at the Maudsley Hospital in London, took charge of during my absence. I think I was lucky to have such reliable people stand in for me, but it took time to pick up the threads. In addition, I had heard whilst I was still at Stanford, that the teaching of pharmacology to medical students in Birmingham had virtually collapsed, and the students were complaining. I won't go into the reasons for this, but after consulting my colleagues, I went to see

the Dean of the Medical School and offered to put on a course in pharmacology for the preclinical medical students. My proposals were accepted and we then became involved in establishing such a course, bringing in people from other departments, where necessary, including clinicians. I had done a limited amount of teaching from the time I received my PhD, but I had felt for some time that we should be doing more teaching. There were also some political and financial considerations. I also found myself on many committees, both university and NHS, some of which had no relevance to my own subject, but as a senior academic, it was considered a duty. At the time, I believe I was the only non-medical head of department in the Faculty of Medicine which, far from being a difficulty, meant that I was frequently asked to serve on NHS consultant appointment committees. They were obliged to have a university representative, and I was told that they preferred to have someone non-medical, who would “have no axe to grind!”

TB: How much interaction did you have with the drug industry?

PB: I did some consulting, but not very much, really. I did not find it very interesting, although I made some good friends in industry.

TB: Was there any particular drug that you had been involved in consultation?

PB: No, the work was more general. I would be asked to look at particular types of research that was going on and advise whether it should continue or stop. I was attending a meeting in Basel on one occasion, and received a call from Hugo Bein, who was head of research at CibaGeigy, and also a friend. Over lunch, he invited me to be a consultant at the firm, and after discussing my role, I accepted. Unfortunately, before my first visit, Bein had left, and the new people had taken over with completely different ideas as to my role, so I did not continue for very long. I also consulted, from time to time, with UK firms such as ICI, Wellcome, and Glaxo, and also supervised research workers in industry, who were allowed to work for a higher degree.

That was quite rewarding. I've always had good relations with the pharmaceutical industry and was happy to advise them, from time to time, on appointments.

TB: You trained many people. Would you like to mention the names of a few?

PB: Well, I have already mentioned Brian Key and Jim Hance, who eventually went to California. Brian remained in Birmingham and was a Senior Lecturer when I retired. There was Tony Nicholson, who was medically qualified, and finished his PhD whilst working at the Institute of Aviation Medicine at Farnborough. During my stay in Stanford, he visited me, accompanied by

a senior RAF psychiatrist. I acted as their guide and accompanied them on a visit to NASA, where I was allowed to try landing a 747 on the simulator! Then there was Malcolm Roberts, who went to Edinburgh to work with John Smythies, and then moved to the Physiology Department in Cardiff. There was also Gill Samuels, who did research on prostaglandins for her PhD. She went into industry, ending up at Pfizer, where she became a vice-president for research, and was involved in the development of Viagra. Ian Phillips went to Ohio University, where I visited him; he is now head of a department at the University of Orlando, Florida. Another was Andy Dray, who worked on opioid receptors. Peter Keane was offered a Royal Society Fellowship to work in Lyon and stayed in France with Synthelabo. There were a number of others, who went mainly into the pharmaceutical industry as academic jobs were getting hard to find.

TB: Could you tell us about your work with opioid receptor?

PB: It came about from a conversation with Hans Kosterlitz from Aberdeen. He admired our work but asked why we had not investigated morphine. I said that we thought morphine was not suitable for iontophoresis, but I was wrong, and when we tried it, morphine produced striking effects which we were able to antagonize with naloxone, the morphine antagonist, applied iontophoretically. Then, came the discovery of enkephalins from the Aberdeen group, which aroused world-wide interest, and we received one of the first samples to test.

TB: So, the research was focused on classifying opioid receptors.

PB: Yes.

TB: Didn't you also do some research with serotonin receptors?

PB: We worked quite a lot on serotonin receptors.

TB: What did you do?

PB: We examined the distribution of neurons that responded to the application of serotonin and its agonists and antagonists.

TB: Weren't you doing also some research with anesthetics?

PB: We were involved in looking at some new anesthetic drugs of the Fentanyl type. They were rather strange drugs and we did not get very far with the investigations, which were supported by a grant from a government department. Those drugs are extremely potent and some are now used

clinically. One of them was interesting because it blocked respiration without affecting consciousness, yet respiration could be started again voluntarily.

TB: Any other research you did that you would like to mention?

PB: None that I can recall at the moment.

TB: It seems that by the 1980s you shifted almost completely to receptor research, right?

PB: Yes, and that continued until I retired.

TB: When did you retire?

PB: In 1986.

TB: Didn't you publish a book around that time?

PB: Yes, it was the book I had started planning when I was at Stanford twenty years earlier, but when I returned to Birmingham, there was little time to finish it until after I had retired.

TB: So, that was in 1986.

PB: It was published in 1987.

TB: Can you tell us something about the book?

PB: It was called an "Introduction to Neuropharmacology." In my teaching activities, which had developed significantly, and included not only medical students, but also dental students, anesthetists working for their primary exams, and postgraduate toxicology students, I felt there was a need for a basic text for such students. That is what the book was intended to be, an introductory text which could also be read by the intelligent layman. Unfortunately, I was rather let down by my publishers. The original publishers I had approached because they were well known for publishing medical books were very keen in having my book after having consulted their advisors and their staff, and were extremely helpful and friendly; my father had worked for them at one time... Sadly, they were taken over by a much larger organization, which although major publishers of science books, were not very interested in my book, although they promised to fulfill the contract. I cannot complain about the production and I was pleased with the result, but I do not think the book received adequate publicity. Not many people I knew said that they had seen the book or even an advertisement for it. I do not think many copies were sent for review, although I received some letters of congratulation, including one from a professor of anesthesiology, and another from a psychiatrist, both of whom said it would be useful in teaching.

TB: It sold quite well. I read it somewhere that it sold about 9000 copies?

PB: I am not sure it was as many as that.

TB: If it was, that was not bad.

PB: I had expected more, but it certainly wasn't a bestseller! There was probably too much competition as everybody feels motivated to write a book these days.

TB: It was probably one of the first introductory books on neuropharmacology.

PB: I think it was.

TB: Would you think that it could still be used?

PB: I would like to hope so. Some parts, in fact most, are still valid, but it would have to be brought up to date, and new sections added. I wouldn't want to do that now.

TB: Was it translated into any other languages?

PB: I don't think so. As I said, the new publishers weren't terribly interested. They fulfilled the basic contract and that was it.

TB: What did you do after the book?

PB: I was still editing the journal, *Neuropharmacology*, and when Costa resigned, I was sole Chief Editor. So there was quite a lot to do, as I did not have any secretarial help. Previously, I had two secretaries and an editorial assistant plus various other people to help me. Then I was asked to join a newly formed International Committee on the Classification of Drug Receptors, which was under the auspices of the International Union of Pharmacologists. I think that this came about because in 1984, two years before I retired, we had a meeting of the British Pharmacological Society in Birmingham. The day before the main meeting started, I organized a Symposium on Serotonin Receptors, inviting everyone I could think of who had worked on serotonin, including its discoverers, Rapport and Erspamer, neither of whom unfortunately was able to attend. We had an excellent meeting and I arranged for the proceedings to be published as a supplement to *Neuropharmacology*. During the discussions, it was suggested that a small group might meet regularly to discuss receptor subtypes, including not only 5-HT, but dopamine and opioid receptors. Subsequently, at the International Pharmacology Congress in Sydney in 1987, which unfortunately I was unable to attend as I was in hospital at the time, a proposal was made to set up an international committee on Drug Receptor Classification, and I was proposed as one of the UK delegates. The committee was small at first and not very active. The chairman was not keen to continue, and eventually Paul Vanhoutte took over. After that, the committee expanded rapidly

and became much more active, producing a series of reports. I was asked to lead a working party on the classification of opioid receptors. It took a long time and involved many people, and at one time, for health reasons, I was obliged to hand over to someone else. Eventually, we published a comprehensive report, which I think, was well received. At one time, the Committee was looking for somewhere to publish its reports, and it so happened, that I was the BPS representative on the editorial board of *Pharmacological Reviews*, and I managed to persuade them to take on the task, so that is where our report on opioid receptors was published...

TB: This was in the early 1990's?

PB: Yes.

TB: Who were the people on the committee? Was Solomon Snyder on it?

PB: No, he wasn't on it. There was Trendelenburg who worked on adrenaline.

TB: Was Sol Langer on it?

PB: Yes, he was. I used to meet him with his wife. He was moving from South America to Paris to be head of pharmacology at a drug company.

TB: Later on he moved from France to Israel. Anyone else on that Committee you remember?

PB: There was Colin Dollery from London, Eric Barnard from Cambridge, who did a lot of work isolating receptors and their constituent proteins, Pat Humphrey from Glaxo, Tom Bonner, Godfraind, Dhawan from Lucknow, and Rudolfo Paoletti. These are the people I remember best, but there were many others, and the membership of the committee changed quite frequently. TB: Could you tell us something about your activities in international organizations. We already talked about the CINP. Haven't you been involved with WHO at a certain point in time. PB: I am not sure of the exact date; it must have been in the early 1960s, before the Birmingham CINP Meeting, that I was invited by the World Health Organisation to join a Working Group on the Major Tranquillizers. When I arrived in Geneva, I was met by the Deputy Director of WHO, a Dr. Medvedev, who took me to his apartment and plied me with vodka, after which he asked me to be the Rapporteur of the meeting. I was reluctant to accept as I had done nothing like it before but could see no way out. In the event, all was well and we had a very successful meeting. I received a lot of help from the other members, including from John Smythies. The only problem was that I had spent every evening after dinner going through the typed transcripts of the previous day's discussions. Lehmann was the Chairman, and the only other members I can remember well were

Deniker and Freyhan. There was also a man named Lapin, a psychologist from Leningrad, who was very friendly and interested in my work, but I never had time to talk to him, as I was so busy with preparing the report. I don't think Michael Shepherd was there, as I knew him well, and would have remembered him. Eventually, our report was published by WHO with the recommendation that the term "Neuroleptic" should be used world-wide, and I think it has been. I was on another WHO committee, which was concerned with amphetamine derivatives that were being made illegally and were popular with drug users.

TB: Could you name one?

PB: One of them was ecstasy. Do you know it?

TB: Yes.

TB: Was this in the '50s?

PB: I think it was 1958, but it could have been later.

TB: Who was director of the mental health unit at the time?

PB: I don't know. A Dr. Chrusciel, if that is the correct name, was working with us on one of the committees, but I don't remember who the director of the unit was. It seemed that staff at WHO changed frequently, but I remember Nakajima who eventually became the Director. I first knew Nakajima when he was working with Thuillier in the 1950s, in Paris. What happened to Thuillier?

TB: He's still alive and writes books.

PB: I think he wrote a book on the history of psychopharmacology but I have not seen it.

TB: I think that at a certain point of time he was involved with the drug industry.

PB: He visited Birmingham on one occasion and gave a talk and showed a film of his circling mice. He had this compound which, if injected into mice, caused continuous circling. I asked him a number of times if he had had it analyzed chemically, and if it was optically active, but I never knew what happened. It was like Monnier's sleep-substance in that respect. He was a very generous man and looked after me extremely well when I visited Paris to meet Delay. Thuillier was a gourmet and took me to some excellent restaurants in Paris.

TB: He was certainly a very talented person: a writer, a pharmacologist, a psychiatrist.

PB: Yes.

TB: Weren't you also on a WHO committee on psychotomimetics, hallucinogens?

PB: I don't remember, but I served on a British Government Committee on hallucinogenic drugs. The Chairman was Bill Paton, who was Professor of Pharmacology at Oxford, and both Ted Marley and I contributed to the report, but what happened to it I never knew. As with so many things connected with government, there was never any feed-back.

TB: In the course of your career, you have been involved, in addition to research, in all kinds of other activities.

PB: Yes, writing, teaching, editing, administration, and even broadcasting, both live television and radio.

TB: You had to take care of people in a rather large department.

PB: It was not that large; but we had many students. Quite a lot of the teaching involved lectures, tutorials, and practical classes and there were postgraduate students to supervise.

TB: We already talked about your book that was published after you retired. Was that your last publication?

PB: No, my last paper was "Classification of Opioid Receptors," which was the report of the working party I had originally led for the IUPHAR Committee on Receptor Nomenclature and Drug Classification. As I was unable to continue at one point due to ill health, the final version was written by M. Hamon, who was a good friend. It was published in *Pharmacological Reviews*, in 1996. The other thing that happened was that I was awarded the Pythagoras Prize from the University of Cattanzaro in southern Italy, which you have probably never heard of.

TB: I read about that Prize in Mimmo Costa's autobiography.

PB: I am afraid that at first I did not take it very seriously, but then I was at a meeting in London and talking to Pepeu from Florence.

TB: Is he a pharmacologist who did a lot of work with cholinergics?

PB: That is right. Anyway, he said I ought to go, as did Costa, who had received the prize earlier. It was a long journey, but I enjoyed my visit and learned more about Pythagoras who lived in that area of Italy for some years with a group of students. He was, of course, a philosopher as well as a mathematician.

TB: What would you think was your most important contribution to neuropharmacology?

PB: It is difficult to think of any one thing. I like to think that we made a number of contributions, perhaps only minor ones, in many areas.

TB: So, you think they are equally important?

PB: I would like to think that the introduction of the microiontophoresis technique for the study of single neurons in the brain is one, and perhaps, our work with opioid receptors and their classification is another.

TB: What about your early contributions about the structures involved in the mode of action of psychotropic drugs?

PB: Yes. I think I made a contribution there, small though it was.

TB: Don't you think that work should have been followed up?

PB: I had hoped it would be. It would have been nice if somebody had done that and, in a way, I thought one of my students might do so, but people like to do their own thing, and why not?

TB: Has research in neuropsychopharmacology in the past decades moved in the direction you would have liked to see it move?

PB: Oh, I don't know. I'm not one of those people who like to foresee what is going to happen or has plans for so far ahead. I just did what I thought was important at the time and what I was interested in. The main thing, I think, is to enjoy what you do.

TB: And you did enjoy it?

PB: Yes I did enjoy it. Also, I think I got on well with the people I worked with; I thought so, but I don't know what they thought! When I retired, a group of my former postgraduate students entertained my wife and myself to dinner at the RAF Club in London, and I shall never forget the student who, when I suggested that he should publish his latest research under his name alone, said "No" he wanted my name on his paper in recognition of the help I had given him. I know also that I valued my stay in Pisa, not just for the facilities and the opportunity to learn microelectrode work, but also because of my contact with Moruzzi.

TB: Could you tell us something about Moruzzi?

PB: Moruzzi was a very nice quiet man. He did not shout as so many Italians do when they get excited, but was very charming, and I think he was an excellent physiologist. There was an unusual atmosphere in his institute which is difficult to describe. The Italian system involved people moving from one center to another for promotion, Rome being the pinnacle, but I do not think that Moruzzi wanted to move from Pisa, as it had everything he wanted, and he had by then an

international reputation. He sometimes asked me to read his papers before sending them for publication, but I found there was nothing I could contribute; his English was better than mine!

TB: Did you maintain contact with him after you left?

PB: Yes, for a while, and then, when he was retiring, they organized a symposium for him in Pisa which I attended. I met some old friends there like Herbert Jasper and Mary Brazier from the early days of EEG.

TB: He was also involved in research on the reticular formation...

PB: Yes.

TB: And in conditioning.....

PB: I believe so.

TB: He was working in Montreal. Didn't you also have some contact with Ted Sourkes, the biochemist from Montreal who wrote a book on the Biochemistry of Mental Disease?

PB: Yes, I knew Ted Sourkes very well. He spent a year in Birmingham at Joel's invitation. Is he still around?

TB: Oh yes, he is retired, but has remained very active. He is editor of a journal on the history of neuroscience, or something like that.

PB: Is he? Oh, that's interesting. Ted used to tell us stories about the institute in Montreal, where he worked and about Ewen Cameron.

TB: But, from all the people you were involved with, it was Joel who had the most important impact on your career.

PB: Yes. He gave me my chance; he started me off in what was then a new field, relating behavior with the electrical activity of the brain, and he introduced me to a lot of people, especially at the neurochemical symposium in 1954 in Oxford. It meant that my work became known rather quickly, perhaps too quickly. He made suggestions, from time to time, but otherwise left me to get on with it. It took me little while to get used to this way of working and we had our ups and downs. I was inexperienced, and I think I resented it when I heard that he was talking about my work to groups I had never heard of. However, he had a way of putting things over much better than I could have done, and the support came in as a result. When he left Birmingham for Washington, I felt neglected, especially as things were in a bit of a mess, but I think it did me good in the end and was an excellent if traumatic experience. Had he stayed in Birmingham, I would probably

have become frustrated and moved somewhere else, where the facilities I had in Birmingham would not have been available, and I should have had to start again.

TB: Just one more last question. Is there anything you would like to see happen in the field?

PB: There has been a trend recently to measure activity at different sites in the brain by means of blood flow. This development is both interesting and important, but it would be nice to see the findings correlated with electrical activity. I had always hoped that someone would extend and improve the techniques which we developed but, so far, that has not happened, as far as I am aware.

TB: So, on this note we should conclude this interview with Professor Bradley, one of the pioneers of neuropsychopharmacology. Thank you very much, Philip for your contributions to the field, and for sharing with us this information.

PB: I've enjoyed it. I didn't expect to, but I have quite enjoyed it.

TB: Thank you.

5. WILLIAM E. BUNNEY, JR.

TB: This will be an interview with Dr. William Bunney⁷ for ACNP's Archives of Neuropsychopharmacology. We are at the annual meeting of the College, in 2001, in Hawaii.

I'm Thomas Ban. Let us start from the very beginning. Tell us where and when were you born, say something about your early interests, education, professional training, and how did you become involved with neuropsychopharmacology.

WB: I was born on June 27th, 1930, in Boston, Massachusetts. After six months, we moved to East Lansing, Michigan, and after eight years we moved to New Jersey, near Princeton. We stayed there until I went off to college in Oberlin. Then, I went to the University of Pennsylvania Medical School; I took an internship at Henry Ford Hospital, and a residency in psychiatry at Yale. After Yale, I had my first job at the National Institute of Mental Health.

TB: When did you decide about medical school?

WB: Very early in high school, in my sophomore year. I had a really great biology teacher. She asked everyone in the class to do a science project. In reading through our biology book, I noticed that they did not know the digestive enzymes in the earthworm, *lumbricus terrestris*. I thought that would be an exciting topic to study so I bred earthworms, dissected three areas of their digestive system and did crude assays for three enzymes. Prior to doing this, I went to the University Library and read up and talked to a couple of experts in biology about the work I intended to do. I found that in fact, no one did know what digestive enzymes there were in the *lumbricus terrestris*. So, I wrote it up and got an A+ on the project and was hooked on science from then on.

TB: That's great!

WB: So that was the beginning of my interest in science. When I was in college, I wasn't sure whether I wanted to go into psychology, psychiatry, or either. I also went through periods of time when I wanted to be a minister. One summer, I served as a minister for a rural community and that was fun. There were three people and four dogs in my first congregation, and by the time I left,

⁷ William E. Bunney, Jr. was born in Boston, Massachusetts, in 1930. He received his M.D. from the University of Pennsylvania and completed his psychiatry residency at Yale. He worked at the National Institutes of Mental Health until he was recruited by the University of California at Irvine to become the Chair of the Psychiatry Department. He was interviewed in Waikoloa Village, Hawaii on December 10, 2001.

two hundred more people had joined. But even though I enjoyed that, I decided very rapidly that I did not want to be a minister. Before finishing college I was pre-med, applied to a couple of medical schools, and got into Cornell University and the University of Pennsylvania. I decided to go the University of Pennsylvania. During medical school, I did some research on the thalamus, none of which was ever published.

TB: Could you tell us something about the research you were doing?

WB: I don't remember the details but it was in anatomy, studying the thalamus in rats. After I finished medical school, I decided I wanted to go into science; so, I went to the National Institute of Health (NIH). My dad had previously hired Jim Shannon, who was then director. He had hired him to head up research for E.R. Squibb & Son, where my dad ended up being Executive Vice President. Jim Shannon headed up their Research Institute and was then recruited from that position to head up the NIH. He was probably one of the most famous scientists to hold that position. My dad got me an appointment with Shannon and I went in to see Jim. I remember it was a hot summer day; Jim was in a totally rumpled seersucker suit and said, "I think you should go back and take your internship, take a residency, and then come back to see me." So I got an internship at Henry Ford Hospital, and about half way through, I began interviewing because I was still interested in psychiatry. I liked it in medical school and in my rotating internship.

TB: Didn't you do your residency at Yale?

WB: I went to Harvard first, was interviewed, but they would have nothing to do with me. So, I went to Yale and they accepted me. But then, I was still interested in many other things.

TB: Like what?

WB: When it came time for me to make a decision on whether or not to accept the Yale appointment, I decided I wasn't going to go; I wrote and told them I was turning it down. I planned to go to Colorado, work in an Emergency Room, ski on the weekends, and finish a novel I was writing. Gene Brody was in charge of Residency at Yale. He wrote me and said, "We've turned down 31 people for this position and if you're not coming, let us know in 24 hours!" I thought it over and figured maybe I could get good material for a novel in a psychiatric residency. So I wrote back and said, "OK, I will come."

TB: What happened to the novel?

WB: I had written half the novel but I never finished it.

TB: Hmm.

WB: After my first day in psychiatric residency, I totally loved it and things moved in a straight line from then on. I came close to not going into psychiatry.

TB: It seems you did. You were interested in writing.

WB: I was; and I ended up doing a lot of writing. I have written over 365 scientific papers and edited seven books. I have also written a lot of poetry.

TB: So you are still writing?

WB: It's on the back burner but someday I will probably do that. All my life, I have written poetry.

TB: OK. So after your first day in residency, you fell in love with psychiatry.

WB: It was love at first sight. I wrote my first paper with Tom Detre, who was at Yale at the time. He was somewhat of a maverick back then; he was saying we should treat patients with drugs when the rest of the discipline was saying we should use psychotherapy and psychoanalysis. I wrote my second paper with Danny Freedman who was also there.

TB: What was the work you wrote up in that first paper?

WB: Tom Detre had developed a vibration machine which we tested. His hypothesis was that sensitivity to vibration was perceived differently by schizophrenic patients. So we did a study where we investigated the responses of normal individuals and the responses of schizophrenics; and, sure enough, the schizophrenic group exhibited a difference in sensitivity to vibration.

TB: Statistically significant?

WB: Yes. We found significant differences.

TB: And that is what you published?

WB: We published the data.

TB: When was this?

WB: Probably in 1959. I remember that because in 1960 I went to NIH.

TB: What about the second paper with Danny Freedman?

WB: We were interested in Rapid Eye Movement (REM) sleep, which was already known at that time. We had one subject we hypnotized, telling her she was watching a ping-pong game. We wanted to see if we could replicate REM sleep with hypnosis.

TB: Did you do the hypnosis yourself?

WB: I did, but this was a very susceptible person. We analyzed her sleep EEG.

TB: By hand?

WB: It had to be by hand back then.

TB: You talked about Tom Detre and Danny Freedman. Was there any other person at Yale you would like to mention?

WB: Another very influential person at Yale was Jules Coleman, who was a maverick and taught psychotherapy. His was a brilliant psychotherapist and had a cult among the residents. After that I applied to the NIMH and they hired me.

TB: As a resident, what kind of drugs did you use?

WB: We were using reserpine and imipramine. Tom Detre was supportive; everybody else thought he was far out.

TB: What about ECT or insulin?

WB: When I took my psychiatry rotation for a month at Henry Ford Hospital, they were using insulin. Every severely sick patient was treated with insulin coma or ECT. In the course of ECT, some patients were regressed down to diapers and bottles. So, these grown people would be put in diapers and given baby bottles. It was amazing.

TB: So, they did regressive ECT.

WB: I don't think Henry Ford Hospital was very progressive, at the time.

TB: What was your first assignment at NIMH?

WB: I was in Lyman Wynn's branch, in Jim Moss' section, in charge of the depression ward. David Hamburg was branch chief at the time.

TB: Was Joel Elkes there?

WB: Yes, and also Fritz Freyhan, as well as Seymour Kety. Kety and Lyman would argue all the time. Bob Cohen was there; he was the person who did everything. He and John Eberhardt hired everybody, they were a team.

TB: Were your activities connected in any way with the research in Joel Elkes' group?

WB: Totally separate. Joe Elkes was at the St. Elizabeth's Hospital. I went there on occasion, but not more than ten times.

TB: Were you one of the first hired for a new program?

WB: Jack Durrell had one ward and I had another; Jack was a little more senior. He was at Yale with me, and when he came to NIMH, he worked with Kety. He had a biological ward and my ward was transitional, not completely biological.

TB: Didn't you work with David Hamburg?

WB: Dave Hamburg and I wrote a paper about a rating scale paper that ended up as a citation classic. It also laid out how you develop and run a research ward. So, it was a methodological paper that probably set criteria for developing research wards around the world.

TB: Where did you publish it?

WB: In the Archives.

TB: So, that was an influential paper?

WB: I think it was. After that paper was published, for the next ten years, scientists who wanted to develop a research ward came and visited us.

TB: Could you tell us about the research you were in charge of?

WB: We collected cerebrospinal fluid, urine, and blood samples and analyzed them for corticosteroids and metabolites of the neurotransmitter-related compounds we were interested in. Collection of those samples went on 24-hours a day. We also developed a rating system, in which the nurses rated the patients every hour, 24 hours a day. So, we had behavioral ratings and biological data we could correlate. We developed an informed consent system that was as good as any developed since. The process involved patients in a group meeting, hearing about the procedure before deciding whether to participate. A patient would say, "I'm supposed to have a spinal tap?" and someone in the group would say, "Oh no, don't do that, it was so painful," and three other patients would say, "I didn't even notice it." That was informed consent! Everybody sitting there talking about the process, giving individuals a chance to make up their mind. Most of them went along with it and some of them would say, "No, I don't want to do that." It was totally different than reading a piece of paper and signing your name. That was a long time ago, before anybody even thought about Institutional Review Boards (IRBs) or informed consent forms.

TB: Yours was a depression ward?

WB: We got the most severe depression cases in the entire metropolitan area. These were really sick, very depressed patients, many suicidal. I remember one research subject, a physicist whom we had on constant urine collection. Whenever subjects left the hospital, they would take their

specimen bottles with them. One winter day, this individual went to a bridge of about a 150 feet elevation and jumped into the water. He left his specimen bottle at the point where he jumped; there was a note, "Please return this to Dr. Bunney at the NIH." Fortunately, he was saved because there was a man in a rowboat who saw him jump, got him out of the ice flow and saved his life.

TB: The research was a kind of group activity; everybody participated?

WB: Right, it was a research team, and in particular, the nurses felt they were a part of the team. There was no question about that. They would argue about the ratings and try to get them right.

TB: Were you using your own rating scale?

WB: We used the scale Dave Hamburg and I developed. A lot of researchers used it.

TB: Could you tell us something about your publications in those years?

WB: In one of the papers we reported our findings on urinary 17-hydroxycorticosteroid levels in 90 patients. In 4 patients, who committed suicide or made a very serious attempt, 17hydroxycorticosteroid levels were highly statistically significantly increased. We always said that should be used as a screen when thinking about whether one should discharge or send a patient out on pass. It was a valid test. It was replicated in three or four studies.

TB: Any other publication you would like to mention from that period?

WB: One early publication was the catecholamine hypothesis paper that also became a citation classic. It was written at the same time Joe Schildkraut wrote his catecholamine hypothesis paper; so there were two papers which were somewhat different.

TB: Any other publications?

WB: Another paper we wrote early was a report on a double blind placebo controlled lithium trial, in which we had one patient whom we took off lithium seven times and each time had a striking relapse. The findings of that study had an effect on the whole field. Our paper came out about the same time as Mogen Schou's. It was a product of the research methodology we used; we had ratings every hour every day. We could see patients receiving placebo got worse, and when put back on lithium, they got better within a few days.

TB: Wasn't it one of the first papers on lithium in the United States with favorable findings?

WB: Before my paper, Sam Gershon, and later, Ron Fieve did work on lithium.

TB: Who were your primary collaborators in those years?

WB: Dennis Murphy, Fred Goodwin, and John Davis. I hired all three at NIMH, as clinical associates.

TB: How long did you run the depression unit?

WB: Ten years, maybe. Later, I was in charge of the Biological Psychiatry branch. Chris Gillin worked with me in those years.

TB: Any other research before you became branch chief?

WB: I did some work with Jack Durrell. Keith Brodie, who ended up being President at Duke, was working with me at the time, before he went to Stanford.

TB: What did he do?

WB: Keith participated in many of our research projects. He published a record number of papers for a clinical associate and still may share the record with Dave Kupfer. It was a very productive period in my life time. There were many people working with me in those years. I once put together a list of scientists and there were 72 collaborators over a period of 10 years.

TB: Seventy-two people!

WB: There were a lot of clinical associates.

TB: Would you like to mention a few of them by name.

WB: The key ones, Goodwin, Murphy, and Davis I already mentioned. Dave Janowsky was another one who worked with me.

TB: Then you became Section Chief?

WB: I became Section Chief, and then, I was on vacation when I received a call. Burt Brown said I want you to be Director of what became NIDA. I went back, talked with him, and decided to do it. So for three and a half years, I was director of Division of Narcotic Addiction and Drug Abuse, as it was called. During that time, my budget went up from \$44,000,000 to \$240,000,000. I had about one thousand people working for me, including the staff at Lexington. That was my PhD. in administration because I was in charge of education, research, and development of the clinical programs, and of all the international interactions. We funded Sol Snyder when he did his opiate receptor work and I participated in the news conference where he and Candace Pert announced the discovery of the opiate receptor.

TB: Where did you move after NIDA?

WB: I had made an agreement with Burt I would be able to go back to the Institute, if I wished, and he honored it. Just about the time I went back, Lyman Wynn left the Institute and I took over

his Branch. I hired a bunch of basic scientists, including Dorothy Gallagher, John Tallman, and Candace Pert, who did outstanding basic work. I also negotiated so that I could develop a child program and I hired Judy Rapoport. Judy came to head up the child program and did a spectacular job. I had a sleep study program with Chris Gillin and a genetic program with Elliot Gershon. So, we put together a genetic program and Judy put together a child program. We had Will Carpenter on the schizophrenia ward before he went to head up the program at the Maryland Research Institute.

TB: What about Bob Post?

WB: Bob Post was there. When I took the job at NIDA, Dennis Murphy was made a Branch Chief and Fred Goodwin was also made a Branch Chief. Then John Davis went to work with Danny Freedman in Chicago.

TB: As branch chief, you created several programs. Could you tell us something about the research in the different programs?

WB: Looking at dopamine metabolites and schizophrenia was a hot area in those years. There were small drug trials that we did. In depression, we tried cocaine, and we used naloxone to see if we could turn off hallucinations but could not replicate the Scandinavian findings. We did some work on dialysis in schizophrenia, trying to replicate others findings. We published a number of negative papers. We looked at GABA agonists in schizophrenia and they didn't work; that still stands. We gave high-doses of diazepam and that did work in some really sick schizophrenics, but it had side effects that made it unusable.

TB: Then you were promoted?

WB: Yes, I was appointed Deputy Clinical Director under Bob Cohen and during the last period before I left the NIH, I was Acting Scientific Director of the entire Intramural NIMH Program.

TB: Why did you leave NIMH?

WB: I felt I needed a new environment, new stimulation. There were a lot of things going on at that point in my life. UCI made me an outstanding offer, and it had as good neuroscience as almost any place in the world. That was very intriguing.

TB: What year was that?

WB: That was 1982.

TB: So, you moved to California and became chairman of the department of psychiatry at Irvine. Did you take anyone with you from NIMH?

WB: Earl Usdin and Monte Buchsbaum.

TB: So you had in mind to continue with your work in imaging?

WB: I got a PET scanner within a year and I still I think it is one of the few PET scanners in a department of psychiatry anywhere in the world.

TB: You have been involved very actively in PET scanning for many years.

WB: Yes. Monte Buchsbaum and I had done the first human PET scan work at the NIMH, and when we went to UCI, we continued that.

TB: What was Earl Usdin doing?

WB: Earl was a master at organizing meetings and editing books. Then he got lung cancer and died.

TB: When did this happen?

WB: Very soon after we went to Irvine. And that was very sad. One hundred and fifteen of the top scientists in the world came to show their respect for Earl before he died.

TB: Can you tell us about your activities after your arrival to Irvine?

WB: It was a learning process. In the beginning, I got a MacArthur grant. That was fine, I was not doing a lot of research but running the department and that's a big job. After that, I stopped running the department for a period, and about three years ago, I picked it up again. I didn't have any NIMH funding until about twelve years ago. Then I got a Center Grant with Ted Jones, who is probably the best neuroanatomist in the world today, and we did a series of ten papers together. We started out by collaborating with other brain banks, and then developed our own and Steve Potkin helped. For the last ten years, we have had a brain bank funded by the NIMH. They funded us to do neuroscience research but we also developed the brain bank. The work that came out of that was quite significant. We showed a decrease in GAD 67 mRNA in schizophrenia. As you know, nothing is ever replicated in schizophrenia, but this has been replicated by David Lewis, and subsequently by three other groups. We did a lot of research with the NMDA receptor and also showed that the subplate cells which move from the ventricular zone to just below the cortical plate were maldistributed in schizophrenia. So, something went wrong during the second trimester

of development. We don't know what but those cells did not migrate to the correct spot. That was done on our Center grant ten years ago with Ted Jones and Schahram Akbarian.

TB: Did you continue with that research?

WB: We continued, and then, three years ago, applied for a Silvio Conte Center grant and received one. For a Conte Center, you are supposed to put together a group of top people. So I got Huda Akil and Stan Watson from Michigan, Ted Jones from UC Davis, and David Cox from Stanford. Cox went to the Perlegen Company, so his co-chair, Rick Myers, of the Human Genome Center came on the grant. The research is going on right now and we are two years into a five-year grant. I have been very interested in genetics for the last four years. I am not a geneticist but I decided the only way to learn it was to teach it. So I started teaching a course to residents and faculty. In order to prepare a lecture, you learn a tremendous amount, including a lot of the language. I am very impressed with microarray technology and had a session here on that. I have developed a major microarray facility, and so has Michigan. Our initial study involved five males and five females. People said you can't run microarrays twice in your own lab and get replicable results. But out of 4,600 genes, we were able to come up with six significant genes and five of those were replicated in all three centers. Then we did RT-PCR that validated it. I presented this at a neuroscience meeting and had a poster there; a scientist came up to me and said, "I spent my life working on mice in terms of male-female gene differences and you've come up with the same genes." We were really excited about that and now have a couple of papers we are working on. Just this month, we finished our first cohort of depressed patients and we have some very interesting genes. We have another couple of months to go because we have to put our three groups together, we have to go through the various cluster analyses of these, and we have to figure out what these genes do. That's just for openers, but within another couple of months, we will be able to look at all 40,000 genes on two chips. It is not out there yet, but we spent four hours talking with Steve Fidor, who is president of Affymetrix, and he says they are definitely going to have this technology. So, we will be able to survey 40,000 genes in the future. We've got a second cohort and Blynn Bunney reviewed about six hundred papers to try to figure out which areas of the brain are implicated in depression. From lesion studies, tumor studies, and a large number of brain imaging studies, we came up with twenty-four areas in the brain. We all get together and work around the clock for about 36-hours to dissect these areas out. So we have about six thousand

pieces of brain tissue from our cohorts, which are labelled with bar codes and frozen at -80 degrees Fahrenheit. I hired Bill Byerley, an outstanding geneticist. You look at the animal models and see what genes are implicated there. Then you factor in what you understand and know about pathophysiology. I call it quadrangulation of information. We screen and validate with microarrays. Let's say you have eight schizophrenic genes, four of which were in hot spots of the genome, three of which were implicated by a drug model of schizophrenia like PCP and happen to relate to dopamine. It's not going to be that simple but that's the idea.

TB: Sounds like cutting edge science.

WB: It is a very exciting time right now. You could not have done this before the mapping of the human genome plus the development of microarrays. We have a superb team working on this.

TB: You put together a new team and you were able to generate the necessary funds. WB: The department is doing very well. Every year, the contracts and grants people publish the amount of money all the departments have in terms of research. In terms of total research dollars, our department ranks #1 out of the 23 departments, above medicine. I am very proud of the people in our department.

TB: You should be. Besides all this, you have been involved in all kinds of international activities during the past twenty years. Would you like to talk about that?

WB: I have been interested in international research all my life but it started with the World Health Organization (WHO) group that Norman Sartorius put together. It was a group of collaborative research programs originally involving about eight countries. We would meet once a year and plan programs. We did genetic and clinical studies, as well as biological studies over a period of approximately ten years. It was quite successful, we all contributed funding and everybody worked pro bono. I really enjoyed getting together with everybody. There were scientists from Russia, England, Belgium, India and Morocco. Alec Coppen, Hans Hippus, and Sol Langer were in it. We would rotate and meet in the various countries to plan research programs.

TB: Would you like to mention some of the studies?

WB: There was this color blindness genetic marker we studied. We did a variety of medication studies, published in top journals. It took a lot of effort because you had to standardize everything and to translate everything into the language of the country studies were conducted in. If you had rating scales, they had to be translated, and then you had to get together and test their reliability.

TB: Did all this start in the mid 1970s?

WB: Yes, and it went on through 1984.

TB: Among your different activities, you also served on many advisory boards. Would you talk about your experience?

WB: I served on the Board of the Max-Planck Institute. I have been on NARSAD (National Alliance for Research on Schizophrenia and Depression) from the day they started and that has been an incredible success story. Three weeks ago, I reviewed this year's applications, and there were 500 from Young Investigators. NARSAD is an amazing organization. The Manic Depressive and Depressive Association has survived lots of problems and is also going strong at this point. I was also on the IBM Medical Advisory Board and the Merck Advisory Board.

TB: What would you consider your single, most important contribution to research?

WB: I would list the lithium studies, the norepinephrine hypothesis, and the one that is in press right now. It is a molecular genetic study in which we have a cohort of fourteen schizophrenic patients, individually matched with controls. TB: Could you tell us more about this study?

WB: I went a number of years ago to Paul Greengard and said, "Let's look at DARRP 32 in schizophrenic patients." He asked me why, and I said that DARRP 32 is regulated by the two neurotransmitters most implicated in schizophrenia. It is reciprocally regulated with glutamate and dopamine and its downstream effect on protein pump inhibition (PPI) is critical for ion channels, neurotransmitters, and transcription factors. He said, "That's great, I have somebody to work on this." It only took us about eight years to do this study, but it is impressive, and it will be published in Archives of General Psychiatry. We found low levels in the dorsal lateral prefrontal cortex and not in other areas and not in other proteins, and they weren't changed by animals chronically on neuroleptics and weren't differentially affected in a couple of patients who were not on neuroleptics. We had a control group of eight Alzheimer's patients, eight on and eight off neuroleptics; there was no difference and they were matched. I think it was a really nice study and took a long time to do.

TB: So, you think these are your three most important contributions?

WB: These were important contributions and I'm sure there are others. Another major contribution is the switch process.

TB: You've received several honors and awards. Would you like to mention a few?

WB: I would say election to the Institute of Medicine-National Academy of Science (IOM/NAS), the Presidency of four organizations; Psychiatric Research; The West Coast College of Biological Psychiatry; The American College of Neuropsychopharmacology (ACNP), and the Collegium Internationale Neuro-Psychopharmacologicum (CINP). The highest honor was certainly the ACNP presidency. I was asked a year ago to be editor of a new neuroscience journal and that is an honor. The most recent award I received was a month ago from NARSAD.

TB: Aren't you a recipient also of the Anna Monika Award?

WB: Yes, I had the Anna Monika Award.

TB: What did you get the Anna Monika Award for?

WB: That was for the write up of the switch process. It was 35 years ago, in the late 1960s

TB: You are still active.

WB: I have the Della Martin Chair of Psychiatry, but I am Co-chair of the Department of Psychiatry, also. And I also have a Distinguished Professorship at UCI.

TB: Is there anything else you would like to talk about we did not cover?

WB: I don't think so. Science has always been exciting and could not be more exciting than right now.

TB: You mentioned at the beginning that you have always been involved in poetry. Are you still writing poems?

WB: Yes, I still write poems.

TB: Have you ever published any?

WB: No, I've received a lot of rejection slips. At one point in my life, I submitted poems to the *New Yorker*, *New York Times*, and *Atlantic Monthly*. You know, the first time they just send you a stamp informing you that you are rejected. Then, they send you a note saying, "rejected." And then, they send you a note saying, "Well, we liked this, but we didn't like" I got to the last stage but I never got to the acceptance stage.

TB: We talked about your papers, but we didn't talk about your books.

WB: I have seven edited books. I may have written one or two chapters in them.

TB: Could you tell us something about the books?

WB: A couple of them were on substance abuse. Jack Barchas and I did one for Earl Usdin.

TB: Is there anything that you would like to see happen in the future in psychiatry and in neuropsychopharmacology?

WB: It's too bad that probably only 40 of the 125 departments of psychiatry have science programs. It would be great if there was a granting system to get them started. I think research is so important for the education of young residents. I would like to see distinct mentorships worked out. Residents don't have to become scientists but they should learn to read a science paper and know how to evaluate new treatments, new thoughts about diagnosis; science is the way to learn that. There is currently a lack of clinical researchers, the NIMH is very concerned about this, and I share their concern. I have been very active with the Institute of Medicine (IOM) and I am currently chairing a committee on suicide, which has been neglected. You have about 5,000 more suicides than homicides in this country, so we are doing a full report on this.

TB: Anything else you would like to add?

WB: I think we've covered a lot. I have enjoyed the interview. I think you have done a superb job, Tom. You are an excellent interviewer.

TB: Thank you. Thank you for sharing all this information with us.

6. ENOCH CALLAWAY III

TB: This will be an interview with Dr. Enoch Callaway⁸ for the International Archives in Neuropsychopharmacology of the ACNP. It is December 1999. We are at the annual meeting of the College. I'm Thomas Ban. You have been involved in neuropsychopharmacology since the field was born. Could we start with your recollections about the introduction of chlorpromazine in the United States?

EC: Right after it became available in the U.S., Smith, Kline & French invited a lot of us to dinner at Trader Vic's. I still remember those thick lamb chops. That was the first time I enjoyed a meal paid for with drug house money.

TB: When and where did you first hear about chlorpromazine?

EC: I think that was at the APA meeting in 1955 or 1956. People were very much divided about it. There were those people who said, "Oh, this drug is terrible. It's going to cover over symptoms, and the patients will never recover. The only way you truly recover from anything is to work it through with psychoanalysis." And there were other people who hailed it as a miracle drug.

TB: What got you interested in psychopharmacology?

EC: I'll tell you a story buried in the archives of dead people's heads. Worcester was the birthplace of the contraceptive pill, and the people there were at the forefront of endocrinological research in psychiatry. I was a resident and research fellow and we had done some studies with schizophrenics measuring cortisol in their urine. That was largely because we could measure cortisol and not many other people could. So we would collect 24-hour urine samples. Our assays were not very sensitive, but you could extract enough cortisol from a 24-hour sample for an assay. The schizophrenics had low cortisols. Later, that turned out to be due to the fact that we studied them in the wintertime when they had scurvy.

We knew that cortisol didn't cure schizophrenia. In fact, it could produce a psychosis. But Armour had extracted and purified ACTH, so Hoagland and Pincus decided that maybe ACTH would cure schizophrenia. Those first doses cost about a half a million dollars, because they were

⁸ Enoch Callaway, III was born in La Grange, Georgia in 1924. He trained in psychiatry in Worcester MA, and then, after enlisting in the military during the Korean War, he worked at the University of Maryland. He moved to the Langley Porter Institute of UCLA where he began research on evoked brain potentials. He was interviewed in Acapulco, Mexico on December 13, 1999.

made from camel pituitaries. It was my job to line up four matched schizophrenics. I thought that from three thousand patients, matching four would be a snap. Well, I learned something about combinatorial mathematics. It took me more than a month to do it, but I ended up with four schizophrenic males, pretty well matched on all the important variables. They looked so much alike you might have thought they were quadruplets. And so, we started our study. Every day, I would rate the patients using the Malamud-Sands Rating Scale. I don't know whether you remember Harry Freeman? He was a very taciturn gentleman, and he would come in every morning with four syringes with peanut oil, two with placebos and two with ACTH. He would inject the four patients and leave. He wouldn't speak to anybody to make certain he was keeping the study blind. Little by little, two of the patients started to improve. They began to comb their hair. They stopped talking about their delusions. They began to look like they were about ready for discharge.

Then one morning the nurse said to me, "Noch, I think that you should look at Bill and John. They're developing acne and humps on their back." Bill was one that we thought was a drug patient, and John was one we thought was a placebo patient. Both were developing Cushing's disease from the ACTH. It took us about another four days to finish up the planned trial, but by that point, our two recovering schizophrenics had regressed rapidly. Almost the whole ward was sitting around in mourning. When the study was done, I remember, I was sitting at my desk, writing up the report and feeling terribly let down. Harry Freeman came in and said, "Cheer up Noch. Suppose by chance it had come out the other way. We could have spent millions of dollars on an ineffective treatment." So, I learned there's something to be said for failures in drug trials.

TB: So, you had been involved in psychopharmacological research since you were a resident in Boston?

EC: Not Boston. There's a saying in Boston, "What do you think of Worcester? As a hole?" I was attracted to Worcester because I was interested in neuroendocrinology, and I did a few neuroendocrinologic studies, but Hudson Hoagland and neurophysiology seduced me away. I can remember Hoagland's first lecture on the EEG, and it seemed to me that this was more likely to tell us what's going on in the mind than measuring steroids in the urine. Before I knew it, Hoagland had inveigled me into becoming the de facto electroencephalographer at Worcester. When I finished my work at Worcester, Jake Feinsinger asked me to come down with him to start the new

department at the University of Maryland. I went to work with him because there were two very good psychoanalytic institutes in Baltimore and I intended to start my psychoanalytic training.

TB: Was this in the early 1950s?

EC: This was in 1950–51. Jake was very interested in having his young people do research, which pleased me. But just before I left Worcester, Sid Sands, the clinical research director, was replaced by a young man named Nate Kline. I overlapped with Nate by about three months, but Nate was an experience, and I still think he was one of psychiatry's outstanding people. God knows he had faults. There was no problem identifying those, but if his critics had done as much good as Nate did, the world would be a better place.

TB: So you moved from Worcester to Baltimore in Maryland.

EC: I moved to Baltimore.

TB: And it was in Baltimore, where you set up your first EEG laboratory?

EC: I didn't do much EEG work there because I hadn't been at Baltimore very long before the Korean War started. The army quickly ran out of medical officers in Korea, and they called up the Navy medical officers and assigned them to the army to become battalion surgeons, which was not a very pleasant prospect. At that time, Jake Feinsinger had a contract with the Army Chemical Center to study effects of anticholinesterase nerve gases. That was supposed to be top secret. I arrived at Edgewood, and Harold Himwich said, "Your work will be secret, but here's *Life Magazine* and if you read this article, you'll figure out what we're doing and where you fit in." When I finished my training at Fort Sam Houston, they began assigning people to different army battalions at the front in Korea. When I went in for my assignment, there were red stamps all over my papers. This army colonel said, "Well, Dr. Callaway, I see you're cleared for top secret." I said, "Yes, sir." He said, "And you know something about chemical warfare." "Yes, sir," I said. For a bleak moment I could see myself as a chemical warfare officer in Korea. Then the Colonel said, "Well, we're sending you back to the Army Chemical Center." So I spent much of the Korean War at the Army Chemical Center, which was a rather unexpected benefit from my interest in research.

TB: So you worked with Himwich in Edgewood and not in Illinois?

EC: I worked with him when he was at Edgewood, before he went to Galesburg. Harold was the director of research for the Army Chemical Center, and one of the more delightful human beings

that it has been my pleasure to know. He and Wilhelmina provided a sort of a constant enthusiastic spirit to our research group. While I was in the military, I noticed some very curious things about the effects of nerve gas on attention. The first job I was given was to measure the nervousness that nerve gas was supposed to produce. Charlie Shagass had developed a method for measuring that, which involved the administering of loud sounds. How much one jumped, seemed to be related to nervousness. So I replicated Charlie's set-up and used his method on people exposed to nerve gas and controls. And lo and behold, the people exposed to nerve gas seemed much calmer and startled less than the controls.

TB: Did you use any electrophysiological measure?

EC: We did electromyograms. We had the person try to hold their arms still, but in a somewhat tense position. Then we blasted 95 db sounds in their ears. Subjects jumped less when they had been exposed to nerve gas.

TB: What did you do after the war ended?

EC: Well, after the war, I went back to the University of Maryland and tried to follow up the observations I had made in the army. At that time, I worked with Bob Grinnell. I didn't get back to EEG for a while because I had a career award in research. I think Danny Freedman, I and another gentleman whose name I don't remember, were the first to get those awards. TB: What were you studying in your research?

EC: As I said before, I was following up the observations I made in the army, and I was also trying to identify drugs that affected startle responses in people. We were looking at drugs like amphetamine, atropine, and scopolamine.

TB: What did you find?

EC: We found that amphetamine did not make people startle more. Now, today, that would not surprise anybody, but then, that's what we were giving it for, to increase startle. In the meantime, the University of California was building a new research wing at Langley Porter Institute. This was just about the time, in the mid-1950s, when I went to the APA meeting, in San Francisco, and first heard of chlorpromazine. My wife, being from Oklahoma, had always wanted to move to California. I had no interest in California, myself, but being a good husband, we went to the meeting. At my wife's suggestion, I called Alex Simon and asked him about job possibilities in California. Alex said, "We are building a new research wing. During the APA, come out and I'll

take you around and show it to you. We've already offered John Lilly the job of chief of research. You know John, don't you?" I said, "Sure." Alex said, "I'll be showing John around and we'd love to have you come along." So I went out to California. Alex showed me around with John. They were building this beautiful, spanking new research wing, and they were going to have four research positions. I said, "John, you're so lucky." He replied, "Yeah, isn't it wonderful?" We parted, and I went back home to Baltimore.

After a couple of days, the phone rang. It was Alex Simon, and he said, "Noch, can you take that job I offered to John Lilly?" I said, "What happened?" He said, "Well, John ran off with the wife of a psychoanalyst from Oakland, and he's gone to the Caribbean to talk to dolphins." I said, "Well, let me come out and talk to you about it." And, of course, my wife was jumping up and down in the chair saying, "Yes, yes!" And so, that's how I got to Langley Porter. My interest in electronics had developed in the course of measuring electromyograms. At Edgewood, they gave me an EEG machine and a Gray Walter analyzer. But it seemed that each time I got the analyzer tuned, it was time to quit work, and I don't think I ever got an experiment run with it. It was a very dicey piece of instrumentation. When I got to California, Charlie Shagass was just beginning to publish his stuff on evoked potentials. I had decided, at this point, that while brain waves didn't seem to be windows on the mind, evoked potentials might be. And so, the Office of Naval Research, the University of California, and the State of California all pitched in and got me started on evoked potentials.

TB: What was your first project with evoked potentials?

EC: The first project was a fairly simple one. When we first got the computers, just being able to see evoked potentials was fascinating, and the early meetings in which we discussed evoked potentials were very much like third grade show and tell sessions, where people say, "Look what I've found," and, "Oh, I've seen something like that before." And nobody knew what any of what we saw meant. But clearly, you could do all sorts of things to the stimulus or to the subject and change the pattern of evoked potentials. And so I thought schizophrenics, if anything, are more variable than normal subjects, so the differences between their evoked responses to repeated tones should be greater than those of normal people. We did a lot of work on that and published a number of papers on it. I collaborated with Manuel Donchin, whose fame rests in his work on the P300 wave.

TB: Are we still in the 1950s?

EC: We are now in the early 1960s.

TB: After Worcester did you get any further training in EEG?

EC: No. After my residency I had psychoanalytic training, and also took math at Johns Hopkins through differential equations; two things that haven't had much value in my work. But, they were sure fun and interesting.

TB: Were your activities restricted to research in your laboratory, or were you also involved in clinical work?

EC: No, my activities were not restricted to lab research. I've always seen patients. I somehow feel my identity as a psychiatrist depends on seeing patients, but I probably have never spent more than half time seeing patients, and sometimes a lot less.

TB: So, at Langley Porter you were seeing patients and doing research.

EC: I was also teaching.

TB: What proportion of your time did you spend seeing patients?

EC: I suppose in those years when grants were easy to come by, I would see patients two nights a week, and when grants got tighter, I would see more. Actually, as director of research, I was not supposed to have clinical duties in the department of psychiatry but was allowed to see patients in the evening. So, I saw patients in the evening and did my work in the daytime.

TB: But your responsibilities included teaching?

EC: Yes, and I was involved with both undergraduates and postgraduates. God knows how research would get done in the United States without graduate students and post-docs. With med students, I probably did mostly clinical teaching. The thing I particularly liked to teach was interview techniques for medical students and residents. They seem to think that they're born with a natural ability to interview patients. But they have to be taught.

TB: Where did your research support come from?

EC: From NIMH and the Office of Naval Research.

TB: Could you talk about some of the research projects you had been involved with at Langley Porter?

EC: One of the main themes that has gone through my work – and I am not so sure now that it was a good theme – was that neurotransmitters would be linked to cognitive processes. I thought

there was some sense, some logic, in the way that acetylcholine seemed to modulate memory, and some sense, some logic in the way that dopamine seemed to modulate attention. As time passed, I got more and more fascinated with that theme and was trying to design tasks that would pull apart acetylcholine and dopamine effects. I was also interested in designing tasks to detect the differences between the effects of drugs; for example, the effects of the benzodiazepine clonazepam and the β -blocker propranolol. When I turned 65, NIH was getting harder and harder to deal with, and the Office of Naval Research said they wanted to fund younger people. They weren't funding anybody over 65. So I moved to the VA, so I could get VA funds for my research. And for a while that worked out pretty well.

TB: Could we get back to your research with acetylcholine and dopamine?

EC: Well, at that time, I thought that different neurotransmitters were associated with different kind of processes in the brain. I thought that there was a grand scheme of things that caused different neurotransmitters to be associated with different cognitive operations. It was only later that Crick, I think, wrote, "There is no grand scheme. God is simply a tinkerer." If I had read that 40 years earlier, I think I would have stuck to neuroendocrinology. But the EEG was very seductive for 'lumpers' like me. I thought we were going to see something that captured what's going on in the mind. I hope the functional MRI people will do lot better than we've done with EEGs. It's been a fascinating field, but I don't think it's very fruitful.

TB: You started to tell us before about your work with evoked potentials in schizophrenia. Could you tell us more about what you did and what you found?

EC: In our early studies, we found that the P300 waves in schizophrenics were of lower amplitude and more variable than in normal subjects. And those were fairly durable findings. We worked with some pretty sophisticated signal detection methodology, but I don't think we got it to the point where it was of any practical use. One of my ex-UCSF colleagues, Alan Gevins, has developed some very sophisticated methods of de-blurring the EEG, literally, making it an electronic lens that looks through the intervening tissues, and combining EEG data with behavioral data. That is very interesting. Don Jewett, who is the guy that discovered the far field evoked potentials, is incidentally another of my ex-colleagues. He is also one of those who quit academia to start their own companies. And Don has some stuff that looks very promising. But, if I had to wipe out a field of knowledge and do the minimum damage to psychopharmacology, I'm not sure

that the EEG wouldn't be my first choice. I remember when Joe Wortis was giving Charlie Shagass' obituary. He said, "Charlie did all the right things in doing research. He just picked the wrong problems." And I think that may be the case here. But some of it seems to be puttering along. Not through me, but through people that were with me, as for example, the work in schizophrenia with Dave Freedman's recovery response, and Dave Braff's startle response. So there still seem to be fruit on branches of the tree, but they are pretty sparse.

TB: What would you consider your most important contribution?

EC: I suppose the students I've worked with. They are probably individually each one worth more than any contribution I made.

TB: Could you mention a few of your students by name?

EC: I was just talking about Dave Braff. I also had Reese Jones. Then there were lots of other people in the lab, such as Bob Freedman, David Servan-Schreiber, Kim Meador, and I don't know whether we should count Jack Mendelson. He was a medical student when I was a resident at the University of Maryland and I supervised him. But I really hate to do this because I'm going to forget to mention someone important. Oh yes, there was Monte Buchsbaum.

TB: Oh, he was your student?

EC: Medical student. Thinking of Monte reminds me of an interesting story. We had what, in those days, were considered outstanding computer facilities. I think we had a computer with 8,000 bits of memory and punch-paper tape, really state of the art stuff. Monte was interested in fluctuation in reaction time. Later, I think that was popularized as the Rabbit Effect. You make a mistake and slow down, and you don't immediately speed up again. It takes a while for the effect of mistakes to wear off. I had been looking for relationships between human cycles, such as diurnal cycles, cardiac cycles, breathing cycles, and variability in the EEG. So Monte learned Fourier analysis in a flash, like Monte learns things, and he asked, "Can I borrow your number for the Berkeley computer?" I said, "Sure," thinking that no medical student is going to run up a big bill on that mammoth Berkeley computer. But Monte disappeared for a week. It wasn't like him not to show up for work. Finally, he came in, and he had six New York phone book sized batches of printout. He had looked at the sequence of reaction times a hundred different ways. This reminds me that Adolph Pfefferbaum, Judy Ford, and Manny Donchin were also in my lab at some time. They were certainly pioneers in the P300 field.

TB: You had been involved in research with the new psychotropic drugs from the very beginning, starting with chlorpromazine. Would you like to talk about some of the drugs you were involved with?

EC: I was doing some research with LSD. We thought that serotonergic agents like LSD were involved in the pathogenesis of schizophrenia. So we did a study with LSD to see if benzyl antiserotonin would inhibit LSD psychosis. We did small studies in those days. We had three nurse graduate students who volunteered to be subjects: one got LSD alone; one got LSD and benzyl antiserotonin; and one got benzyl anti-serotonin alone. It was a double-blind study but we thought that it was immediately apparent who got what. One girl started to have florid hallucinations, one complained of headache, and the third didn't notice anything. So we said, "Well, the gal with the headache got the benzyl anti-serotonin; the gal with the florid hallucinations got the LSD; and the gal with nothing is the one who has had her psychosis blocked by the benzyl antiserotonin." Wonderful! I had someone stay with each one of them all night.

But the girl that didn't have any symptoms said to her monitor, "Look, I'm just very tired and I don't want you sitting around. Would you go and leave me?" And the lady, against all my instructions, left. That evening, I got a call at home from the head nurse. "You've driven one of my nurses crazy. She's sitting in front of the television set talking to it." I said, "Oh, shit. I'll get in the car and come in." I broke the blind, of course. The one that had the benzyl antiserotonin alone was the one that had the florid hallucinations in the lab; the one who had the headache had been given LSD; and the one hallucinating in front of the TV had LSD and benzyl antiserotonin. So, benzyl antiserotonin didn't do anything for LSD psychosis, but the power of the placebo effect was incredible.

I still hope that somebody will find there is some logic to psychopharmacology in terms of neurotransmitters. As a clinician, I have become less and less hopeful. Every so often, I see a patient who has failed on three SSRIs, abysmally, and when I put him on a fourth he gets well beautifully. If all four drugs have similar neurotransmitter effects, that doesn't make much sense. In fact, I'm still convinced when I see a serious obsessive patient who gets well on an SSRI that the old psychoanalytic theories of obsession made much more sense than the fact that they respond to a drug. You know, you could make such wonderful analytic interpretations about the content of the obsession.

TB: It looks like you are not very much impressed with SSRI antidepressants.

EC: Oh, I'm very impressed with them. But I'm not impressed with the theories.

TB: Do you remember your first publication?

EC: I think the very first thing I published was on cortisol output in the course of electric shock treatment.

TB: That was work done in Massachusetts?

EC: In Worcester.

TB: Where was it published?

EC: I think it was published in the *Journal of Nervous and Mental Disease*, which was a good journal in those days. Then I had a series of papers on schizophrenia with Monte Buchsbaum, Manny Donchin, Reese Jones, and Dave Braff. Toward the end of my research career, I got very interested in parallel distributed processing and neural network modeling, and I still think that something is going to come of that. One of the last papers I wrote was on neural network modeling to explain amphetamine effects. But then, I think that the more recent work that Jonathon Cohen has done in the same area of research is much better and probably makes what I did quite obsolete.

TB: But it was your work that opened up the field of neural network modeling. Could you talk about your contributions in that area?

EC: Well, I don't want to take any credit for developing it at all. The credit should go to David Servan-Schreiber, who came to work in my laboratory. The idea I had was that each neurotransmitter has some unique global effect on cognitive processing. I was hoping one could design a network that would model changes in human behavior, produced by changes in a particular neurotransmitter, with changes in a particular parameter in the network. The neural networks are fairly simple arrangements of hypothetical modules placed in layers which interact with each other by either inhibition or excitation. You can take a very, very simple arrangement and model some amazing things, as Jonathon yesterday presented in his Stroop model, which I think has three layers and four neurons in each layer. It's very simple. Jonathon is not talking about norepinephrine, serotonin, and other neurotransmitters. He's now talking about brain structures. And his notion that the frontal cingulate gyrus is a feedback loop that is responding to conflict makes a lot of sense to me. As for which neurotransmitters are operating in the frontal cortex, there are GABA, glutamic acid, norepinephrine, serotonin, and probably some others we don't even

know yet. So, I think that looking for anatomical analogies to neural nets is going to be much more promising than looking at neurotransmitters. If I wasn't retired, I would get involved with people doing fMRI and neural net modeling to try and relate structures to functions.

TB: You are retired, but aren't you still involved in developing new drugs with a drug company?

EC: Are you referring to memantine?

TB: Yes. Could you elaborate on that?

EC: The drug company is called Neurobiological Technologies. Currently memantine is available in Europe. We are doing some work in neuropathic pain with it, and we shall soon break the double blind to see what happened. We have "very promising results" with it in Alzheimer's disease, and the company is making a big splash about that at the Alzheimer meeting in Stockholm. So that's been a lot of fun. We started out with Nancy Lee and Horace Loh to work on dynorphin, but that has fallen by the wayside. I had a theory that turned out not to work. I thought that if you combined physostigmine and scopolamine you'd have sort of an imitation of nicotine effect that would help people stop smoking. But it did not work either. And every failed drug trial is about 10 million dollars down the tubes. But we may make it. We still have some work going on with the corticotropin-releasing hormone that seems to combat edema in a very curious way. It reduces peritumoral edema, it reduces post-surgical edema, and we're now looking at what else it does.

But my favorite hobby now is treating patients for the Family Service League, where I don't get paid, and so I don't have to worry about managed care. Most of my patients are on welfare, so if I want to try a new drug, all I have to do is deal with the pharmacist who oversees the program. He and I now have a cordial relationship, and I can almost get anything for my patients. So, it's fun.

TB: When did you first get involved in new drug development?

EC: I suppose when I was at Worcester. We did a study there giving methamphetamine to schizophrenics. There was a controversy whether methamphetamine would make them worse or better. And we found that it activated them, but it didn't necessarily make them sicker. They were just more active. Then, as I mentioned before, I was interested in benzyl antiserotonin. And later on, I became very interested in what might be called nootropics. I was also working with MDMA before it became illegal, primarily to open people up for psychotherapy. It was an incredible agent.

TB: Do you think that MDMA is particularly suitable for opening up people for psychotherapy?

EC: Yes, and also some other amphetamine analogues.

TB: Are you still interested in psychotherapy?

EC: I guess what I'm interested in is the mind, and how you study it, regardless whether listening to a patient, or giving a drug, or looking at an evoked potential. One of my teachers once said that a lot of people are not interested in psychology and psychiatry because they are naturally intuitive and they know what is going on in people's minds. And there are others of us who are essentially psychologically tone-deaf, and we have to work to understand it. So for us, it isn't intuitively obvious what's going on. We are puzzled why it happens in one way and not in another. And I'm one of those people who are constantly puzzled by what is going on in somebody else's mind.

TB: And you would use any means to understand it.

EC: Yes.

TB: From all the different means you have tried which one would you trust the most?

EC: I think that what we are seeing now is a convergence of different methods, a combination of cognitive testing, drugs, fMRI, evoked potentials and others, and I feel kind of sorry for the new generation. They will need to be physicists, mathematicians, psychologists, and pharmacologists all at the same time. We used to talk about interdisciplinary research, and the idea that there is some underlying general principle that brings all these disciplines together. We thought that by getting the mathematician, the physicist, the physiologist, and the psychoanalyst in the same room together, they would find the secret. One of the wonderful little phrases that came out of these brainstorming sessions was Karl Pribram's. He said, "Emotion is the ablativ of motion. If you hit somebody, you don't experience the anger quite as much as if you sit still." But modern research is big business. Just look at the slides people present now. They say, "This is the team that worked with us," and there are four columns of names.

TB: What was actually your last publication?

EC: My last paper was published in the *California Fly Fisher* and was entitled "Two psychiatrists look at their obsession." I don't think it's going to be picked up by Medline. The last one before that was on the effect of cotinine, which is a metabolite of nicotine, on behavior.

TB: When was it published?

EC: About one and a half years ago.

TB: What are you doing these days? You have your clinical practice, and it seems that you are advising Neurobiological Technologies.

EC: And I do fly-fishing.

TB: And fly-fishing? When did you become a member of ACNP?

EC: I don't think I was there at the very first meeting, but I think I was at the second one.

TB: So you became a member soon after it was founded, in the early 1960s?

EC: Yes.

TB: Were you ever an officer?

EC: I was on the Council.

TB: So you had been a counselor. Have you been actively involved with any other professional organization?

EC: Yes, I was involved with the Society of Biological Psychiatry. I was president of that organization, at one point.

TB: So you were active in the Society of Biological Psychiatry.

EC: Yes. Joe Wortis was one of my favorite human beings. I was also president of the Society for Psychophysiological Research.

TB: Would it be correct to say that your primary area of research was psychophysiology?

EC: Yes.

TB: And you have been interested all through your career in new psychotropic drugs?

EC: Well, I'm trying to keep up with the new drugs for my small practice. As a matter of fact, a lot of people don't know that there is a listserv on the World Wide Web, which is run by Ivan Goldberg, in New York. There, one can find information that is usually not reported elsewhere. They describe difficult cases and their responses to drugs.

TB: So, you think that we are missing some important clinical feedback.

EC: Yes. There is a lot of what we could learn from uncontrolled research.

TB: You have been involved with psychopharmacology for almost 50 years. Do you think we have made major advances since the 1950s?

EC: Well, I have been interested, lately, more in history than before. I guess the older you get, the more interesting history becomes. During the past 50 years, the other major event in psychiatry besides the introduction of psychotropic drugs was the community mental health movement. There

are some interesting books on that. *Madness in the Streets* is one of them. It raises the issue that de-institutionalization started well before the introduction of the new psychotropic drugs. In fact, I remember that already at the time I left Worcester, there were teams looking for patients to discharge. The idea that patients can be kept out of hospitals and treated at home is not new. But with the anti-psychiatry people, it has led to the denial of mental illness with detrimental consequences, because if there is no mental illness, there is no need to put up money to take care of psychiatric patients. So the state hospitals were closed or drastically reduced in size. And now in the United States – I don't know what Canada is like – but the state hospitals are being reopened as forensic institutes, because the only way that some people can get treated, if they are seriously ill, is to commit a felony. Unfortunately, long-term results of involuntary treatments aren't so good.

TB: In your evaluation, what was the contribution of new psychotropic drugs?

EC: Well, we don't see those chronic depressed patients and totally beat out obsessive-compulsives we used to see in the state hospitals. I think the big problem in depression is how to get primary care physicians to recognize anxiety and depressive disorders. Those disorders now are treatable; the problem is how to get physicians to recognize them. The other day, I saw a friend, whose doctor had just said, "Well, you're 75 years old. Everybody is depressed when they're 75 years old." This is the opinion of a 45-year-old physician. Now, how do you educate these people?

TB: So, we have made progress insofar as we don't see those chronic depressive and obsessive-compulsive patients. On this note we should conclude this interview with Dr. Enoch Callaway.

Thank you very much for sharing this information with us.

EC: Well, thank you. You are a very gentle interviewer.

TB: Thank you.

7. WILLIAM T. CARPENTER, Jr.

TB: This is an interview with Dr. William Carpenter⁹ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. We are at the Annual Meeting of the College in San Juan, Puerto Rico. It is December 10, 2002. Let's start from the very beginning; where and when were you born? Tell us something about your education, early interests, and activities.

WC: I was born September 15, 1936, in Jacksonville, Florida. Before long, my family moved back to North Carolina, where both my parents came from. I grew up in a small town in western North Carolina called Rutherfordton. I went through the public school system and then to college. I selected one of the colleges that offered to pay scholarships for football and basketball. I enjoyed sports as a nice way to work my way through college. I went through the Wake Forest University Medical School and interned at the North Carolina Baptist Hospital in Medicine. I trained in Psychiatry at the University of Rochester. John Romano was in his heyday and it was a fantastic place to learn how to be a physician-psychiatrist. I finished training, in 1966, and went to the intramural program at NIH. Biff Bunney had started a Depression Unit and I worked with a very exciting group of people for the next two years on that Unit, and then stayed on in the NIMH Intramural Research Program (IRP), working with the World Health Organization International Pilot Study of Schizophrenia.

TB: How did you get into psychiatry?

WC: I went into psychiatry and medicine because I took aptitude testing and the psychologist looked at my histogram and told me "you have no talent in music," which is true, but I don't know how he knew that. He then said, "It means you want to go into medicine and specialize in psychiatry." You can't get that information from tests, but that is what he told me. So, that's how I decided to go into psychiatry.

TB: I see.

WC: So, I went to college knowing I was going to be a psychiatrist. It was almost the same when I went from Rochester to NIMH. I knew I wanted to get into academic medicine and need to do

⁹ William T. Carpenter, Jr. was born in Jacksonville, Florida in 1936. He graduated from Wake Forest School of Medicine and completed his residency training in psychiatry at the University of Rochester. Subsequently, he worked in the Intramural Program of the NIMH before moving to the Department of Psychiatry at the University of Maryland. He was interviewed in San Juan, Puerto Rico on December 10, 2002.

some research, first. That was no doubt Romano's influence. One wished to be something that Romano would approve of and it seemed like the way to do that was to go get your feet wet in research and do some publishing. I published one paper from work I did in Rochester, but that was just a case study.

TB: When was it published?

WC: It was probably published in 1967.

TB: What was the paper on?

WC: There was an old gentleman I saw in the emergency room who had become psychotic and ended up in a nursing facility. He had incipient dementia but was well adjusted at home. He went for an eye exam and became psychotic. So I looked into what drug they put in his eye and found there had been old reports of people having a psychotic reaction if a concentrated solution of that substance was used. There were no reports of psychosis with the dilute solution he received. So, I wrote it up as a first case of psychosis at the approved concentration.

TB: What was the drug?

WC: I don't remember. It was used to dilate the pupil. The reason he didn't recover was that his adjustment to dementia was so frail he wasn't able to go back to living independently. I sent the paper to the Archives of Ophthalmology and they accepted it.

TB: Could you tell us more about Romano? It seems he had a great impact on your career.

WC: Romano was a towering intellectual figure in psychiatry. He took a great interest in his residents, met with all of us regularly. We each had a chance to bond with him and model after him. He was very particular about our training, our program and the people in it. George Engel was the other major influence in Rochester at that time. He espoused the biopsychosocial model. But, with Romano, it was a relationship that I was able to keep up over the years and in his later years, saw a lot of him. He was a very influential person, and more than anything, he was a critical thinker, open to all things in psychiatry, as long as you thought critically about them. So, it was truly a broad education, very patient centered. Rochester did not have much strength in research at that time, although Bob Ader was there, launching the field of psycho-immunology. George Engel's group looked at developmental issues. There was a strong interest in certain psychological issues in terms of vulnerability to different diseases.

TB: So, this was your background before you went to NIH?

WC: Yes.

TB: So you arrived to NIH and started in the Intramural Research Program.

WC: I started off in a fairly large office occupied by Dave Anderson, Fred Goodwin, John Davis, and Dennis Murphy, and David Janowsky came the next year. That was the group working together on that unit. William Bunney was head of the program and Jim Maas head of the section. Jim moved to Chicago a few months later. Lyman Wynne headed the Adult Psychiatry Branch. I went originally for two years but I wanted to stay on and shifted over to work on schizophrenia in a project with the World Health Organization. I worked in that with Lyman Wynne, John Strauss, and John Bartko.

TB: Before you moved to work on schizophrenia, you said you worked with Biff Bunney.

WC: I spent two years on Bunney's Depression Unit. I had asked to work with Biff Bunney, because George Engel was very impressed with the work Biff was doing. Lyman Wynne had given a talk in Rochester and I had asked to be in Biff Bunney's group.

TB: What did you do?

WC: Well, there were two main lines of work Biff was interested in that Dennis Murphy, who arrived at the same time, and I should be doing. One was on lithium and electrolytes. This was before lithium was on the US market. The other one was on the hypothalamic-pituitary adrenocortical axis. Biff assigned Dennis to lithium and electrolytes and off they went. I was asked to run the clinical unit and work on the hypothalamic-adrenocortical axis. This was a nice choice for me. I enjoyed the clinical unit; I wasn't really prepared to be a researcher. Jan Fawcett preceded me in working with Biff, and Jan and Biff had written a blueprint for working up the HPA system in depression. With the blueprint in hand it was not difficult to figure out a series of studies. Other studies involved suppressing the HPA axis with dexamethasone. We had negative results on the hypothesis that depression was associated with failed dexamethasone suppression of adrenocortical release. When I presented the data, Barney Carroll was in the audience and pointed out we dosed at midnight instead of at eleven PM. He was right; this probably explained our negative result. We looked at the circadian rhythm of cortisol and I found some alterations in the daily rhythm. We found a burst of increased cortisol levels around REM sleep, but the lab values were difficult to believe, and we did not report this finding. It was right about that time that Ed Sachar reported the episodic bursts in cortisol release. I'm almost sure we were actually

seeing those episodic bursts. We also did metabolic clearance rates. This was an interesting series of studies, but we were not able to confirm an abnormality in the HPA axis in manic or depressive disease, except the alterations in circadian rhythm. I think we did not do the dexamethasone suppression test correctly. The main impression these studies made on me was they could not address causation. Almost any alteration in this stress sensitive HPA axis could be secondary to depression rather than a causal pathway. It didn't suit me to continue in these projects. I don't know why, but my interest was more in schizophrenia. So I talked to Lyman Wynne to see if there were any other positions in the Branch. I had actually asked Lyman about working with him on his family studies and extend it into depression to see whether there was evidence of thought disorder and communication deviance in families of people who were vulnerable to depression with psychosis. I remember Lyman saying, "Well, sure, that would be real interesting. We can do that in the context of the International Pilot Study of Schizophrenia (IPSS)." Of course, we never did. My assignment was to work with John Strauss. Lyman asked John to head up our group. That was in 1968, and it turned out to be a remarkable experience.

TB: Could you tell us something about the IPSS?

WC: In 1968, it seemed everybody in the world knew how to diagnose schizophrenia except American psychiatrists. The comparison of US and UK had made clear that in the United States there was over diagnosis of schizophrenia. The difference may have been overestimated since the US sample was from the New York City area. Paul Hoch's influence with concepts such as latent schizophrenia and pseudoneurotic schizophrenia were in vogue. Diagnostic patterns were different as you moved south and west, but European psychiatrists had a lot more interest in specific approaches to diagnosis. The IPSS was set up using John Wing's Present State Examination (PSE), based on identifying nuclear schizophrenia, using Schneiderian first rank symptoms. So, I'm a young person working on this study. John Strauss is two or three years older so you've got these two young Americans and Lyman shepherding us. We learned how to do a systematic interview, but John and I thought schizophrenia too complex to be characterized by symptoms. We did not understand the postdictive and predictive power attributed to the nuclear schizophrenia construct; or how special diagnostic symptoms achieved a classification with such robust reduction in heterogeneity. We argued, no doubt inadequately, for the inclusion of developmental, social, and other behavioral assessments. We were not persuasive enough with our international collaborators.

There was little interest, no time for added measures, and they didn't see any need. If you knew how to diagnose nuclear schizophrenia they insisted, you picked up the background pattern that predicted the future course. So, we quickly put together a prognostic scale based on work by Norm Garmezy, Joe Stephens, and George Valliant. These prognostic data were only collected in the US cohort. The IPSS plan was to do two year and five-year follow-up studies, but eventually, Ann Pulver and I did an eleven-year follow-up on the US cohort. We argued that in assessing outcome, you need to assess occupation, social outcome, and things other than psychotic symptoms we thought were important. And again, the investigators from other countries believed mapping symptom course with the present state examination was sufficient. That was an era when, in clinical trials, the only things measured had to do with the psychosis. You might measure a time to discharge or a time to readmission in a maintenance study, or just measure symptoms. The whole concept was that if you measure the psychosis you're pretty much capturing the disease. So, for studying the US cohort, we developed the Strauss-Carpenter Level of Functioning Scale to assess a variety of functional outcomes in addition to the measures included in the original protocol. Schizophrenia is not good for anybody, but it's not a uniform, or a progressive deterioration in most patients. With the developmental data, the symptom data, and the outcome data we collected, we identified three domains of psychopathology in people who have a diagnosis of schizophrenia. Each of these different domains had its own history and its own future. The past predicted the future within each domain but told almost nothing about the other domains. Even the best measures of psychosis told us nil about the social or occupational course of the disease. If you want to know whether a person is likely to be employed in the future, you get their past work record. You don't measure psychosis in order to predict function. Based on our observations, we proposed that within the schizophrenia syndrome, individuals have different combinations of pathology. Those different domains are relatively independent from each other. We don't understand why they are co-occurring, but it may be that they have a different etiology and pathophysiology. We also observed that almost all schizophrenia patients had reality distortion such as hallucinations and delusions but not all patients had dissociative thought disorder. You could meet criteria for nuclear schizophrenia without having thought disorder. Some patients had negative symptoms and others did not. We focused on negative symptoms by identifying six pathologic features first, then reducing the six features to a three component model comprised of

positive psychotic symptoms, negative symptoms and pathology observed in the interpersonal context. We treated these three domains of psychopathology as independent. We were quickly learning a lot about Schneiderian first rank symptoms, extensively used in Europe and the rest of the world in diagnosing schizophrenia, and about Langfeldt's system, in which true schizophrenia and schizophreniform reaction were separated, seemingly validated by poor outcome in the former and good outcome in the latter. We were able to test these systems, at the time when DSM III was being formulated. Influenced by Washington University, DSM III has placed heavy emphasis on reality distortion symptoms and ego boundary disturbances, emphasized by Schneider and Langfeldt.

TB: Could you tell us about Schneider's "first rank symptoms"?

WC: Schneider posited that certain psychotic symptoms, referred to as "first rank symptoms" were pathognomic of schizophrenia if they occurred with a clear sensorium. Helm Sterlin described that Schneider, when interviewing, asked the patient about these first rank symptoms. He would say, "Are you hearing your own thoughts aloud?" Or, "Are voices talking about you in the third person?" In our work, in the context of the nine-nation study, we found that first rank symptoms occurred in other disorders, as well. Our findings challenged the dominant single disease paradigm and introduced a new conceptual approach to schizophrenia pathology.

TB: Would you like to say something about the Flexible System Criteria you developed for diagnosing schizophrenia?

WC: We derived, empirically, the most robust system, the Flexible System, for distinguishing between nuclear schizophrenia and broad-based schizophrenia by analyzing the data from our US Center, then from all nine participating countries, to determine the most discriminating symptoms. John Strauss, John Bartko, and I did a discriminate function analysis in half the patients and derived the most discriminating symptoms among cases with psychotic features, and then tested the derived system in the second half of the cohort. The results were basically the same and we reported our findings, the Flexible System Criteria (FSC), in *Science*. Seymour Kety referred to the FSC as the first empirically derived and validated diagnostic system for schizophrenia. Our findings are once again disproving the nuclear schizophrenia hypothesis. Three of the most discriminating symptoms were poor rapport, poor insight, and restricted affect. We argued for their inclusion in DSM-III, but the response was that DSM-III was being based on evidence. Much

of the evidence was a belief that the Schneiderian approach defined Kraepelinian schizophrenia, which we had disproved in our follow-up studies. The DSM-III approach seemed destined to enshrine first rank symptoms as the way to diagnose schizophrenia, and by doing that, it transformed schizophrenia into a reality distortion syndrome. DSM-IV-R has attempted to correct this with negative symptoms included in the diagnostic criteria.

TB: What would you say we learned from your studies?

WC: Our studies led to an appreciation there are different components of schizophrenia that run different courses, that prognosis is not based on the ascertainment of special psychotic symptoms, and that reality distortion symptoms, even special forms of it, are common in psychosis and not of much prognostic significance. These data, and the conceptual framework that evolved from them, have profound implications for clinical trials and the assessment of therapeutic efficacy. It has been slow coming, but there is now general recognition that antipsychotic drugs are not anti-schizophrenic. They have efficacy for psychosis, the reality distortion and disorganization domains, but not for negative symptoms and cognition impairments.

TB: What are the implications of your findings?

WC: If you look in the literature, even today, virtually every post-mortem, neuroimaging, treatment, or genetic study is designed as though schizophrenia is a single disease. At the Maryland Psychiatric Research Center, a group of us have divided schizophrenia according to the presence or absence of primary negative symptoms, referring to the two groups as deficit schizophrenia and non-deficit schizophrenia, and we got remarkably robust differences between the two groups with functional and structural neuroimaging. Kraepelin classified dementia praecox as a single disease, despite observing “two groups of maladies”; and Eugen Bleuler established the single disease paradigm with his concept of the dissociative pathology being fundamental to all cases. The field has been slow to break with this dominant paradigm, but we see increasing interest in the domains of pathology paradigm. For example, the current interest in treatment of negative symptoms and cognition impairments as two separate components of the illness.

TB: Could you say something about the people involved in the IPSS?

WC: Mort Kramer at NIMH was a terrific influence in the field of schizophrenia from an epidemiologic and public health vantage. He had been involved in the US-UK study which suggested that schizophrenia was similar in New York and London, but diagnostic practice was

quite different. The findings prompted the World Health Organization and NIMH to determine if schizophrenia was similar or distinctive in various cultures and John Cooper was the PI of that study. Mort Kramer and Marty Katz were important on the NIHM side, and Lyman Wynne was asked to advise and organize the US site. Dr. Lin from Taiwan was then at the World Health Organization and was initially PI of the IPSS. Norman Sartorius succeeded him as PI. The nine centers were; London, Aarhus, Moscow, Cali, Agra, Ibadan, Prague; Taipei, and the US Center at NIMH. John Wing, author of the Present State Exam, was important in initiating and conducting the study.

TB: When did you leave the NIMH intramural research program?

WC: I was in the intramural program for nine years, leaving in 1975. We had a series of studies with several collaborators and were beginning to address the heterogeneity problem of schizophrenia at the level of biology, psychophysiology, and clinical phenomena. When Lyman Wynne had left to take the Chair in psychiatry at the University of Rochester, Biff Bunney had come back to head the Adult Psychiatry Branch.

TB: Where did you go?

WC: I went to Einstein, in the summer of 1975, and came back to Maryland in the winter of 1977. I did not accomplish much in research during the brief New York time, but did begin to address the confound between primary and secondary negative symptoms.

TB: Primary and secondary negative symptoms?

WC: That concept we published, in 1974. We reduced symptom pathology to three components; positive psychotic symptoms including reality distortion and disorganization of thought; negative symptoms described in Jacksonian terms; and pathology that was best seen in a social context, such as poor rapport. This new paradigm was based on the semi-independence of these components within individuals and within domain consistency between developmental history, episode presentation, and future course. Then, in 1982, two papers came out that were very influential. Andreasen had done an analysis with two very important observations, one wrong and one right. She and Olson found that hallucinations and delusions segregated together, and were separate from disorganization, forming two separate pathologic domains. This observation is correct and has been replicated many times. But, Andreasen and Olson also found an inverse relationship between negative and positive symptoms and proposed these as two subtypes. This

was a mistake, because this inverse relationship between negative and positive symptoms has not been observed in most studies. Classifying on the basis of positive and negative symptoms is too state dependent. For example, on admission with florid psychosis, a patient would be classified as positive schizophrenia and at follow-up, with psychosis reduced and negative symptoms more apparent, the same patient would be reclassified as mixed or negative. Tim Crow proposed Type I and Type II schizophrenia as two diseases, in 1982. This was also very influential; the two types were distinguished by the presence or absence of primary negative symptoms. This approach was similar to our proposal. Crow also hypothesized certain treatment response and pathophysiologic differences between the two types, but that has not been validated. According to his hypothesis, Type I schizophrenia was associated with dopamine pathophysiology and response to antipsychotic drugs, whereas Type II was based on structural pathology and was not responsive to antipsychotic drugs. Empirical studies have reported more evidence for reduced volume of structure in the hippocampus in Type I schizophrenia than in schizophrenia with primary negative symptoms. Our approach to it would be to say that the positive psychotic symptoms occur in both, and in both conditions, they are responsive to antipsychotic drugs. The really unfortunate aspect of the negative symptom story is that the field has made a complete mess of the concept by non-valid ascertainment procedures. A person with schizophrenia may have negative symptoms, such as restricted affect, alogia, anhedonia, and low motivation and social drive for many reasons. If they are a direct result of the schizophrenic pathology, these are considered primary. But a patient may be socially withdrawn if paranoid, or if enthralled with reality distortion symptoms. Restricted affect might be the result of drug-induced akinesia. Anhedonia may be a result of depression or demoralization. The rating scales commonly used in psychopathology studies or to measure change in clinical trials do not distinguish negative symptoms based on cause. Anhedonia was an important pathologic feature of schizophrenia as put forward by Radó and by Meehl. But the construct involved a diminished capacity for reinforcement, reward, and experience of pleasure. It was not a temporary loss of ability. Normal humans in grief have a reduced ability to experience pleasure, but not a trait loss of capacity. On rating scales, depressive anhedonia would not be differentiated from schizophrenic anhedonia. This failure to differentiate primary from secondary negative symptoms has resulted in today's debate as to whether antipsychotic drugs have efficacy for negative symptoms. If you get a group of depressed paranoid patients on high doses of Haldol

(haloperidol) then you have depressive anhedonia, akinesia, psychotic withdrawal, and paranoid guardedness resulting in high negative symptom ratings. If you treat the psychosis effectively, especially with a drug that does not induce dysphoria or akinesia, the negative symptom ratings will be substantially reduced. This is the case whether or not the person actually has any primary negative symptoms. So, with all the first generation antipsychotic drugs, the negative symptom ratings would suggest we've got a good treatment for negative symptoms just like we do for psychosis. And with second generation drugs being less likely to cause secondary negative symptoms, they sometimes appear to have superior "efficacy" for negative symptoms. But this is a pseudo-specificity problem that the FDA is keenly aware of, with the result that no superior efficacy claim has been granted for negative symptoms. So, we worked out a method for distinguishing primary from secondary negative symptoms. Some argue that researchers cannot determine whether negative symptoms are primary or secondary. The answer to that is, if a patient comes in with a flat emotionless face, you need to figure out if he's got Parkinson's disease, if he has drug induced akinesia, or if it is depressive anhedonia, because we have differential treatments for these conditions. Brian Kirkpatrick led the work in preparing a schedule for the detection of the deficit syndrome. We did a series of studies that relate to the validity of splitting schizophrenia, according to presence or absence of primary negative symptoms. The question is whether you would get differences between the two groups. Should I go into that?

TB: Yes, please.

WC: At the Maryland Psychiatric Research Center, we found that we could reliably divide schizophrenia into deficit and non-deficit groups. Doing so, resulted in interesting clinical differences. For example, the non-deficit group was more likely to be involved in substance abuse, more likely to experience depression, and more likely to be suicidal. Brian Kirkpatrick, who has done a lot of work on this, observed that while the two groups were similar in having delusions, the group with primary negative symptoms was less likely to have a social content to the delusions. Bob Buchanan did a series of neuropsychological studies, which suggested these two forms of schizophrenia may have different etiologic pathways. The deficit patients with restricted affect are less likely to experience distress. Another important step involved glucose PET imaging. Carol Tamminga used this technique to identify the involvement of anterior cingulate anatomy in the psychosis domain. We, then, separated patients into deficit and nondeficit schizophrenia. Most

regions of interest did not distinguish schizophrenia subjects from normal controls, but the anterior cingulate differences were present in both schizophrenia subgroups. However, the remarkable finding was the robust reduction in resting glucose metabolism in inferior parietal and prefrontal cortical areas in the deficit subgroup. Non-deficit schizophrenia was similar to normal control values in these regions. This was a categorical, not a quantitative difference, and did not appear related to severity. More recently, Adrienne Lahti and Henry Holcomb, as well as Carol Tamminga and I, have been able to repeat these studies using Oxygen 15 in the presence of a discrimination task; and it looks like deficit and non-deficit schizophrenics use their brain differently in accomplishing the same task. The difference is seen in the involvement of inferior parietal and prefrontal cortical areas. A number of other neural integration measures also separated deficit from non-deficit schizophrenia. With this evidence, and support for several aspects from other investigators, we made the provocative claim to have met the hundred year old challenge to determine whether schizophrenia is a syndrome comprising more than one disease. In any case, we summarized the evidence supporting the hypothesis that deficit schizophrenia is a separate disease, in the Archives of General Psychiatry. We are involved in determining if this subgroup is distinguished using post-mortem gene expression data. It is clear that the domains of pathology are critical at the treatment level. This is especially important in drug discovery, because fifty years of creating antipsychotic drugs has not resulted in drugs with therapeutic efficacy for impaired cognition or primary negative symptoms. Even with clozapine, all studies that have separated primary negative symptoms have failed to document efficacy. In cognition, beneficial effects may be more apparent than real.

TB: So, you are saying that clozapine is not superior on primary negative symptoms?

WC: Not on primary negative symptoms. The drug may show superior antipsychotic effects, but the negative pathology is not treated. To put it bluntly, fifty years of antipsychotic drug development has not resulted in efficacious treatment for the aspects of schizophrenia that account for poor functional outcomes. Our domain of pathology paradigm predicts that across domains, efficacy is unlikely, but drug development has been dominated by the single disease paradigm with psychosis the focus of drug development. From the domain vantage, it seems evident that a different developmental model is needed for discovery within each domain. It is good to have drugs with a more favorable effect on negative symptom ratings. But this is quite different than

having efficacy for what Kraepelin described as the avolitional component of the illness, and what we refer to as primary negative symptoms. And, I would use a parallel argument with cognitive impairments in schizophrenia. Cognition advantages of second generation antipsychotic drugs are importantly dependent on excessive dosing with haloperidol in the comparator group and/or commercial sponsorship of the study. We need new models for developing novel treatments! I could be wrong, of course. But if I'm wrong, I'm only slightly wrong. No one thinks there is a robust difference between old and new drugs. So, from the standpoint of drug development, it really calls for new ways to discover molecular targets for drug development to benefit cognition and primary negative symptoms. The psychosocial treatments, incidentally, and this is not our work, have been proven efficacious in schizophrenia. It seemed to work at the level of psychotic symptom reduction and prevention of relapse, in the same areas that are best affected by antipsychotic drugs. Psychosocial treatments are not documented as efficacious for cognition or the primary negative components of the illness. Hogarty has the most promising and comprehensive approach in this regard.

TB: What would you suggest?

WC: We do need new approaches. First, take the domains model seriously and determine domains of interest for drug discovery. Each domain lends itself to developing partial animal models. Etiologic information can also be used to create animal models and determine what domains are manifest. Greg Elmer, Jim Koenig, and Michael Vogel are doing this at the Maryland Psychiatric Research Center. Jim has used the mid-trimester insult epidemiologic data to create a model in the rat. Relevance to schizophrenia is validated with a number of behavioral, physiologic, and genetic variables. Second, reduce the heterogeneity of schizophrenia in genetic, neuroimaging, and post-mortem studies with the domains approach, or with the application of genotype data. This can increase the robustness of any hypothesis testing. If there are several pathophysiologic pathways in the schizophrenia syndrome, we can expect neuropathologic findings to relate to some, and not to all, cases. We have been encouraged in this approach by increasing the robustness of neuroimaging findings, and by identifying subgroups with gene expression data. Third, reduce the heterogeneity of genetic studies by linking each involved genotype with a phenotype. Any drug developed, based on genotype information, can best receive proof of concept testing in the involved phenotype. Testing in a schizophrenia cohort with mixed phenotypic make-up, risks type

II errors. Fourth, many elements of cognition are impaired in schizophrenia. These elements are dissociable and are good leads for animal model development.

TB: What is your current research?

WC: At present I am PI on a four center, NIMH funded clinical trial, with Bob Buchanan, Dan Javitt, Steve Marder, and Nina Schooler. We are testing negative symptom efficacy hypotheses and cognition efficacy hypotheses for an agonist and a partial agonist at the glycine site on the NMDA receptor complex. I am involved with programs establishing design and assessment procedures for testing cognition and selecting suitable candidate drugs for testing.

TB: Could you tell us something about the Maryland Psychiatric Research Center?

WC: Al Kurland, whom I think was a charter member of the ACNP, headed a research unit at the Spring Grove State Hospital. He founded the MPRC as a state mental hygiene administration facility. This included basic science labs and office space. The program opened in 1966. I accepted the appointment as Director, in 1977. After a very vexing start, this has become a labor of love. At the outset, there were no clinical facilities, and the scientific staff was not prepared for a future in schizophrenia and neuroscience research. It had been over five years since an MPRC scientist even applied for a grant. The decision to focus on schizophrenia was easy, for that is what I knew and what the program needed. I believed I could not attract good clinical scientists without a strong neuroscience program, and vice versa. I also wanted people to be independent scientists and to reach for their own farthest star. Rather than one or several of us determining the entire scientific agenda, I felt we could rely on a group of scientists in a geographically isolated center to provide synergy and integration, as opportunity occasioned. This seemed the ideal formula for translational research and creative productivity. I have been very surprised with how well this has worked.

TB: Could you tell us about your activities in ACNP? When did you become a member? What would you consider your most important contribution to the organization?

WC: I became a member around 1978 or 1979, after coming to the MPRC. I became a fellow in 1981. Prior to that, my work in psychopathology would not have been viewed as central to neuropsychopharmacology. The first grant I received related to psychopharmacology was for a clinical trial of hemodialysis, a hot topic in the late 1970s. The results were negative, and publication in the *New England Journal of Medicine* was influential. Since then, I have done

clinical trials with NIMH support on carbamazepine, diazepam, mazindol, targeted antipsychotic treatment, dose reduction with fluphenazine injections every six weeks compared to biweekly, and the current study with glycine and d-cycloserine. I enjoy the meetings and have served on several committees, but don't know if I contributed much. I have now started serving on Council, and this work seems very important. I am particularly interested in how we manage relations with industry, address conflict-of-interest issues, and how we establish credibility as an independent source of expertise on neuropsychopharmacology issues.

TB: What would you say is your most important contribution to science?

WC: I think the Maryland Psychiatric Research Center. I started with a building on a state hospital campus, and have been able to attract terrific people, whose collective contribution to the science of schizophrenia is very substantial. As for specific research contributions, I think the paradigm shift with domains of pathology, defining deficit schizophrenia as a putative disease entity within the schizophrenia syndrome, and distinguishing primary negative symptoms and getting the field to focus on unmet treatment needs.

TB: Is there anything else you would like to add?

WC: No, if you think we've covered everything.

TB: I think we did. This concludes our interview with Dr. Carpenter. Thank you very much.

8. CHARLES JELLEFF CARR

TB: We are in Nashville, Tennessee. It is July 19, 1999, and this will be an interview with Charles Jelleff Carr¹⁰ for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let us start from the beginning.

JC: I started my professional career in the Department of Pharmacology of the University of Maryland. After 20 years with the University of Maryland, I moved to the Department of Pharmacology of Purdue University but stayed there only for about two years.

TB: Could you tell us something about your activities during those years?

JC: Well, John Krantz and I wrote a textbook in the late 1940s

TB: What was the title?

JC: The Pharmacological Principles of Medical Practice.

TB: When was it first published?

JC: In 1949, and then revised in 1950, 1951, 1952, 1953, 1954 and 1958.

TB: Who was the publisher?

JC: Williams and Wilkins. It became a very popular textbook, and it sold very, very well, but had to be continuously brought up to date. And, I just got tired of it.

TB: So, the first edition was published in?

JC: 1949.

TB: And the last edition?

JC: In 1958.

TB: Whose idea was it to write a textbook?

JC: It was John Krantz's idea. John and I worked together and we coauthored the book.

TB: Was the book translated into any other language?

JC: Oh yes, it was. It went into several different translations in other countries.

TB: I know there were Spanish and Portuguese translations.

JC: I think that's right.

¹⁰ Charles Jelleff Carr was born in Baltimore, Maryland in 1910. After earning a Ph.D. in pharmacology at the University of Maryland in 1937, he held faculty positions at Maryland and at Purdue University, before joining the Psychopharmacology Service Center of the NIMH, in 1957. He later edited the journal *Regulatory Toxicology and Pharmacology*. Carr died in 2005. He was interviewed in Nashville, Tennessee on July 19, 1999.

TB: So you had the first edition in 1949 and the last in 1958.

JC: It had to be revised almost every year, and I had to spend my whole time to keep the stuff going.

TB: Yes, indeed.

JC: Textbook writing is a very laborious task because the field is changing so rapidly all the time that one can't keep up with it.

TB: By the time of the last edition, you moved from the Department of Pharmacology at the University of Maryland to the Psychopharmacology Service Center (PSC).

JC: Oh, yes.

TB: Why did you move from the University?

JC: I met Jonathan Cole at the National Institutes of Health (NIH), and I was attracted to this whole new field. I didn't know anything about it, but I learned pretty rapidly.

TB: What was your position at the Center?

JC: Senior Research Pharmacologist.

TB: What did you do at the Center?

JC: I was responsible for the Pharmacology Unit. We had to do a lot of things in those years because the whole subject of psychopharmacology was foreign to the thinking of physicians and people in general. It was a very unique moment in history, I think. You know that.

TB: Yes.

JC: It was believed for hundreds of years that when people got crazy that was the end of it. Now we were saying that one can give them a pill and they will get better. People did not believe us, and that was a problem.

TB: During the years you were with the Center, a steadily increasing number of new psychotropic drugs were released for clinical use in the United States and all around the world.

JC: Yes. The pharmaceutical companies were first skeptical about these drugs, but later on they began to jump on the bandwagon and were trying to see what their beneficial effects might be.

TB: What did you think about these new drugs?

JC: Well, I was excited about them as a pharmacologist. They were drugs with potential benefit for psychiatric patients.

TB: Were you teaching pharmacology in those years?

JC: Well, yes, but while I was working at the Center, I was not doing any outside teaching. And at the Center, we did not do any research with the new drugs.

TB: Weren't you the one at the Center who was reviewing the pre-clinical aspects of grant applications?

JC: Oh, yes, I did that. People were expecting explanations about how these new substances were working, but we didn't know much about that in those years. It was also a challenge to me because I did not know anything about psychiatry. We were also working with people who came from other countries. There was that wonderful man who came down from Canada.

TB: Heinz Lehmann?

JC: Yes, Heinz Lehmann. He was a genius and I will never forget him. Heinz came down one time, and I remember very, very well, we were both in a little group meeting, and he said, "You know I was walking across the campus of the University of Utah, and I saw some dandelions, and I wondered about those dandelions, they go to sleep and then they wake up, and I wondered why. Why would a dandelion close up and open up again?"

TB: And, then he tried to see how dandelions respond to drugs.

JC: Oh, that was it? I remember a picture of him in a hotel with dandelions in a glass of water.

TB: He gave drugs to them.

JC: He did that. It was a novel approach, a very novel approach.

TB: For how long were you with the Center?

JC: Six years. During my stay, I wrote a paper on psychoactive drugs with Jonathan Cole that was published in 1959 in a volume on Research in Psychopharmacology in Children, edited by Seymour Fisher. And then, I had a paper on psychopharmacology that was published in the Encyclopedia Britannica in 1959.

TB: You left the center in 1963?

JC: Yes, that was about right.

TB: Why did you leave?

JC: Well, I don't think I had a particular motive for leaving.

TB: You became the Chief of the Scientific Analysis Branch of the Life Science Division in the Army.

JC: Oh yes, I worked with Colonel Huber for several years.

TB: Then you moved to the Life Sciences Research Office of the Federated Societies for Experimental Biology?

JC: The movement from the Army to the Life Sciences Research Office was really an extension of the program in the Army. They financed that office, but we were not in the military.

TB: So, that was a continuation of your work in the Army. Weren't you director of the office?

JC: Yes.

TB: It was during those years that you became involved in food safety.

JC: That's right. There's always the opportunity to embrace something novel that hasn't been done before. In 1979, we had the opportunity to really develop a food safety council.

TB: And you also developed standards of safety for drugs.

JC: No, at the time it was primarily safety of food ingredients. The agricultural industry was very concerned about that, because there had been a lot of claims that food was not good and had bad things in it. So we had the opportunity then to establish a food safety council to investigate that kind of problem. And that was working very well. It was about ten people that constituted our original group. I had to get them together, make arrangements for meetings with them, and we had to come forward at the end, whether one or another foodstuff is safe, or no. It became a big job that went on and on for a long time and I was looking around for help. I needed a good, competent secretary and I was very fortunate in being able to find one. It was through my secretary that I met Sallie Carr. We married and have been happily together for 19 years, and that's about my story.

TB: You have not mentioned the journal *Regulatory Toxicology and Pharmacology*. Weren't you the editor of the journal? How did that come about?

JC: My friends, who were always looking for jobs for me, came and said "Look, a new journal is going to be published by Academic Press in California and we need somebody to be the editor of that journal. I said I didn't want to do that: "I don't want to go to New York; I don't want to go to Washington; I don't want to go anywhere." And they said, "You can do it right out of your own home." I said, "How do you do that?" They said, "You can have an office in your home." Well, that's when I met Sallie. You met Sallie, my wife. And Sallie said, "I figure that's a good idea. Let's try it." So, we did that and the darn thing took off. Now I get so many manuscripts coming in that I work from early morning till night. We work very, very hard. We have a beautiful office in our home. The journal was growing faster than we wanted. It's the price of success. I guess.

TB: And, you are the editor-in-chief of the journal, right?

JC: That's right. Well, I get the manuscripts that are submitted for possible publication and then I have a whole bunch of people that I use as peer reviewers. I look at the manuscript and I pick out two peer reviewers and the manuscript goes off to them. Very rarely they come back with, "That's a great thing; publish it; go ahead." It happens that one reviewer says, "It is great, publish it," and the other one says, "It's terrible, don't publish it." That's also rare, though. Usually they have some kind of objection or suggestion for doing such and such, and they lay it out for me. Our role is only as an intermediary. The manuscripts then go back to the authors and they have to decide whether they will do the suggested revisions.

TB: So, the journal keeps you very busy.

JC: If I had not had Sallie to help me out, I wouldn't have been able to do it.

TB: As editor-in chief, you are working with a group of people.

JC: Well, out of the journal, in 1984, grew an organization known as the International Society of Regulatory Toxicology and Pharmacology. It is composed of scientists, who give their time and effort to evaluate for companies whether their products are safe and should be pursued for approval by the Food and Drug Administration. Products, especially in the medical field, have to be approved by the Food and Drug Administration. So, the companies come to our group and ask us to give them an opinion about the safety of their products. It may save them a lot of work. The companies have their own scientists who do reviews for them, but they like an outside person, who is independent, who can give them their opinion. We do a little bit of that. It's a lot of work, but, anyway, it's also a lot of fun. We don't make any money out of it, but it's nice to be able to do that.

TB: How many members do you have in the society?

JC: It's a small organization, has always been small with about 250 members from around the world. I would say that, at least 200 are domestic and from Canada and the rest come from elsewhere. We hold annual meetings; we usually try to hold at least one meeting and, if possible, we have a second or third. Now this year alone, we have already had two meetings, and are anticipating a third. We have dealt with the Food Quality Protection Act, in March that is going to be published in the journal.

TB: Who is organizing those meetings?

JC: Sallie, my wife. Some of those meetings are quite small. We had one on DNA (deoxyribonucleic acid), in 1995, in Florida, with about 20 in attendance. The report was written up, and then published in our journal. So now, four years later, we've been contacted and asked if we would now hold another meeting on DNA.

TB: In most of your meetings you evaluate whether one or another product is safe.

JC: Yes, that's right.

TB: And you publish the reports of all those safety evaluations by your group in the journal. JC: We don't publish all the reports. Some of the reports are confidential. The firm pays the money to bring the scientists together. We are sort of an intermediary.

TB: Intermediary?

JC: Our role is to organize the meeting and to give them a report on what transpired at the meeting.

TB: I understood from you that the society is international.

JC: Well, yes, but most of our members, as I indicated before, are from the United States.

TB: Who are the people involved?

JC: Most of them are well known scientists from the pharmaceutical or food industry. I don't think I can name them all. We have a lot of them.

TB: That's fine. What would you consider your most important contribution?

JC: Well, I got an award in the mid-1980s from the University of Edinburgh for my work on chemical anesthesia, the history of chemical anesthesia. TB: So you had also been involved in chemical anesthesia.

JC: Long time ago, John Krantz got me interested in the nature of anesthetic agents, and for my review I read all the literature related to the discovery of the anesthetics. At the time, they were first discovered no one knew that if you put a person to sleep by the inhalation of an anesthetic, or suspected anesthetic, that they would ever wake up again.

TB: A last question: Are you still continuing with the journal?

JC: Yes.

TB: In concluding, I would like to add that your work has had a major impact on toxicology.

JC: I like to think that.

TB: Thank you for sharing this information with us.

JC: Okay.

9. KANELLOS D. CHARALAMPOUS

TB: We are at the 38th annual meeting of the American College of Neuropsychopharmacology in Acapulco, Mexico, at the Acapulco Princess Hotel. It is December 14, 1999, and I will be interviewing Dr. Kanellos Charalampous¹¹ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let's start from the beginning.

KC: I grew up in Greece, and I lived there until the age of nineteen. I grew up during difficult times. In 1940, the Nazi forces invaded Greece, and in 1944, when the Germans were still occupying the country, the civil war was already in progress. Communist guerillas tried to take Greece. My family was religious and right wing, and we were exposed to quite a bit of danger. My father, a physician, was practicing in an area controlled by communist guerillas. Since he did not join them, we were looked at as enemy. The civil war ended, in 1949, and the same year I finished high school. I went to Athens to attend simultaneously the University of Athens and Panteios University. I studied philosophy, theology, and political science.

I came to the United States during Christmas 1950, directly to Texas, without knowing anything about Texas. In January 1951, I started college at the Texas Christian University, majoring in biology and chemistry. I graduated, in 1954, with a double major. During my college years, I took several courses in marine biology and received a fellowship to study oyster mortality. In those years, there was a legal battle in Texas between the oyster growers and the oil companies. The oyster growers complained that the drilling offshore was killing the oysters. The Judge asked the opposing parties to bring forward research findings. Biologists were hired by the opposing parties to pursue research as to the cause of oyster mortality. I received a stipend from Humble Oil Company and went to Virginia Marine Institute as a member of a team of biologists on the defense side. I had my oyster trays in the James River. I also took a course in fish biology at William and Mary.

During my junior year in college, I decided to apply to medical school. Since I was a foreigner, I could not apply to state schools. I had to apply to private schools and I was fortunate

¹¹ Kanellos D. Charalampous was born in Athens, Greece in 1931. He received his M.D. degree from Baylor College of Medicine, in Houston TX, where he also completed his residency in Psychiatry, and eventually, joined the faculty. He subsequently had faculty appointments at the University of Oklahoma, Southwestern Medical School, and Texas Tech before returning to private practice in Houston. He was interviewed in Acapulco, Mexico on December 14, 1999.

to be accepted by Baylor College of Medicine, in Houston. In 1954, I started medical school and graduated, in 1958, with an M.D. After the first year in medical school, I had to work because I could not receive any money from home. I got a clinical clerkship in the Houston VA Hospital, and was assigned to assist two psychiatrists. One was Dr. Charlie Gates, who was doing a study with chlorpromazine, and the other was Dr. Alex Pokorney, the director of psychiatry at the Houston VA Hospital. I did the statistical evaluation for their studies. Actually, in Houston, studies of chlorpromazine had begun before 1955. In 1953, Professor Eugene Khan at Baylor, a student of Emile Kraepelin, had read in the French literature the papers of Laborit, Delay, and Deniker, and he communicated this information to John Kinross-Wright, a Professor of Psychiatry at Baylor. John Kinross-Wright began clinical investigations with Thorazine (chlorpromazine). Kinross-Wright was also studying another compound, NP207, that was abandoned later, because it caused pigmentary retinopathy. Kinross-Wright was a very good clinician. He started a psychopharmacological research center at Baylor that was one of the six psychopharmacology centers at the time in the United States.

When I was a student at Baylor, I did a fellowship with Dr. William Spencer, a pioneer in rehabilitation. The study was on the oxygen consumption of polio patients using respirators. I also assisted Professor Arthur Keats in the clinical evaluation of new compounds in the control of postoperative pain.

Between 1958 and 1959, I completed my internship at the city hospital of Houston. At Baylor Medical School I had two great professors. One was Hebel Hoff who discovered the physiograph. The other great professor was Michael E. DeBakey, my professor in surgery. As a freshman, these professors impressed me with the idea that the complete physician should be a clinician, a researcher, and a teacher. I was debating whether to stay in the United States or go back to Europe. I decided to stay in the United States and thought that the new frontier should be in brain diseases.

I started my residency in psychiatry at the Baylor College of Medicine and affiliated hospitals. One good thing that happened in Texas, in 1949, was the establishment of the Psychiatric Institute in Houston. It was a state facility. The plan was to upgrade the Public Health System in Psychiatry in Texas with an institute for research and training. The original plan also included the establishment of two other Institutes, one in Dallas and one in San Antonio. These, however, were

not funded. The one in Houston was funded, and was directed by William T. Lhaman, who later became Professor and Chairman at Cornell. Dr. Lhaman put together a very good program for the Psychiatric Institute, and in the 1950s, he encouraged Dr. Kinross-Wright to develop psychopharmacology. The program in psychophysiology at the Institute, directed by Neil Burch, was also a strong one. He was pursuing research in sleep and did period analysis of EEG. I had an elective in research while I was a resident. I had to make a decision whether I should work with Dr. Neil Burch or Dr. Kinross-Wright. Dr. Neil Burch was very easy going and Dr. Kinross-Wright was aloof. I decided that psychopharmacology would be more interesting to pursue. Dr. Kinross-Wright gave me a drug to work with that had only been studied in small animals before. It was the enanthic ester of fluphenazine. I gave it to dogs first, and then, to monkeys. In 1962, I took it to the psychopharmacology unit at the Texas Department of Corrections in Huntsville and carefully, I gave it to human volunteers. I concluded that fluphenazine enanthate, in doses of 25 mg in one cc. of sesame oil, when given to patients with schizophrenia would decrease their symptoms. I also found that its clinical activity could last up to two weeks. These observations were followed up by a controlled study, first in which, fluphenazine hydrochloride was compared to fluphenazine enanthate, and later, by a study of fluphenazine enanthate in maintenance therapy and relapse prevention.

When I finished my residency, I joined the faculty of psychiatry at Baylor and was appointed as associate chief of the psychopharmacology center at Baylor. This center had several inpatient units but no outpatient unit. I suggested to Dr. Kinross-Wright that we complement the center with an outpatient clinic. One day, unexpectedly, he said, "Let's go to Austin and talk to the Superintendent of the State Hospital." Patients from Houston had to go 164 miles away to Austin for their psychiatric inpatient care. We visited with the Superintendent, Dr. Sam Hoerster, a sensitive and caring physician, and he agreed to send the patients from Houston upon discharge to our new outpatient clinic. I directed the clinic for three years, from 1963 to 1965. Controlled studies confirmed that aggressive aftercare with medication maintenance could reduce rehospitalization significantly.

TB: Did you publish your results with fluphenazine enanthate?

KC: Those results were published, in 1964, and then some of our later results were published, in 1965. In 1963, I had also started to do basic research. I was interested in studying mescaline. I

went to the nuclear medicine department, got experience in isotope studies, and got my license to do isotope studies from the Atomic Energy Commission. I used isotopes in clearance studies primarily with newer antipsychotics, but also with antidepressants. I did clearance studies with tritiated protriptyline, thioridazine, haloperidol, and mesoridazine. I used ^{14}C in my studies with mescaline and did the definitive study on the metabolism of mescaline in man. Those studies were published in *Psychopharmacologia*, in 1965 and 1966. I presented the data also in one of the early symposia at the ACNP meeting in San Juan, Puerto Rico.

TB: Could you tell us something about your findings?

KC: We identified all the metabolites of mescaline, and then, we tried to see if any of them were active. That was not the case. By the time I completed the studies with mescaline, a report appeared in literature by Arnold Friedhoff on a “pink spot” he found, allegedly in the urine of schizophrenics, only. He claimed that it was not present in the urine of non-schizophrenic patients. From the literature, we surmised that the “pink spot” was dimethoxyphenylethylamine. We got the substance, got it isotope-labeled, and gave it to human volunteers. We found that its largest metabolite in the urine was an acid. We studied it also in plasma and spinal fluid. I gave dimethoxyphenylethylamine to human volunteers and found that it has no activity. I gave it in a dose as high as 11 mg per kilogram of body weight. To decelerate the breakdown of the substance, I pre-treated the subjects with a monoamine oxidase inhibitor. There was no activity. These findings were published in the *Journal of Pharmacology and Experimental Therapeutics*. Two years later, Arnold Friedhoff published a similar study in mice. To my surprise, our paper was not included in his references. In any case, the hypothesis about the role of the pink spot in the etiology of schizophrenia could not be substantiated.

TB: So, you were the first to study the effects dimethoxyphenylethylamine, and among the first to question the theory that schizophrenia is the result of an endogenous, toxic, catecholamine metabolite.

KC: Right. As you recall, in those years, there was also a great deal of interest in the study of indoleamines and β -carbolines. In the Psychiatric Institute, there was a biochemist who was studying β -carbolines. This particular line of work had not proved useful. With Dr. Kinross-Wright at Baylor, we did several studies with phenothiazines, tricyclic antidepressants, and hallucinogens. I did not take part in any of the studies for the defense establishment. Altogether, I participated in

about one hundred clinical studies. Many of these studies were not published because of the desire to publish only controlled studies, or those with positive results. I think we made a mistake. They were primarily late Phase I and early Phase II studies. In retrospect, we should have published more of them.

TB: Can you recall just a few of the drugs you worked with at the time?

KC: Most of them were phenothiazine analogues; many were antidepressants and indole amines. We did some studies with dopa decarboxylase inhibitors, together with monoamine oxidase inhibitors, and we did studies with methyldopa and α -methyl-paratyrosine. We did also some studies with GABA.

In 1965, we had a new Director at the Psychiatric Institute, Dr. Shervert Frazier. Dr. Frazier initiated significant epidemiological studies in the state hospitals in Texas. Prior to his arrival, a new law, House Bill 3, for the care of the mentally ill had passed in Texas. The law was signed, in 1963, by the governor of Texas, John Connally. John Connally had considerable sensitivity for psychiatric disorders. He did, I think, two great things for Texas. He created a board of higher education for the state that upgraded the university system. He also created a very strong basis for subsequent development in computer science and industrialization of the state. Also, he used House Bill 3 to upgrade the mental health system in Texas, by appointing Dr. Frazier, mental health commissioner. When Dr. Frazier permanently returned to the eastern United States, Dr. Kinross-Wright succeeded him as mental health commissioner.

I decided to leave Baylor and went to Oklahoma, to work with Dr. Jollyon West, a flamboyant psychiatrist. He had, before my arrival, inadvertently killed an elephant from the Oklahoma Zoo, overdosing him with LSD, while trying to produce a model psychosis. The elephant had two convulsions, fell over, and died.

In the department of medicine at the University of Oklahoma, there was a strong clinical pharmacology division. Doctors Colemore and Clark had a clinical psychopharmacology program in the prison system at McAllister, Oklahoma and another one in the Central State Hospital in Norman, Oklahoma. I participated in some of their studies.

When I was informed that Dr. Jollyon West was moving to UCLA, I decided to leave Oklahoma. I went to Dallas and joined Southwestern Medical School, ostensibly to help with the development of a psychiatric research institute. I continued with my studies in

psychopharmacology there and did some research with benzodiazepines. One of the substances I worked with was clorazepate. I had negative findings. This particular drug did not prove to be successful in the market place.

TB: In what dosage did you use clorazepate?

KC: I think I used up to 30 mg; I thought it would be sufficient. While I was in Dallas, I became the Clinical Director of the Woodlawn Hospital, an affiliate of Parkland Hospital. It was a seventy-bed hospital for the psychiatric care of adolescents.

Before I went to Dallas, I made a trip to Geneva to meet with officials of the WHO drug abuse section. From there, I went to Turkey and Greece and Morocco to study marijuana/hashish and to interview both users of hashish and health care professionals. When I came back to the United States, I gave a number of talks about marijuana/hashish. I had also gone to the British Museum to study the six volumes of the Royal Hemp Commission, a report on India's use of marijuana. With this information, I invited a panel of experts for a section meeting of the American Psychiatric Association in Boston, in the mid-1960s. I invited the most significant persons in the control of drug abuse in the United States. These people came happily to Boston to discuss the dangers of marijuana use. While the meeting was going on, the doors burst open, and students from Harvard and Boston University came in and the meeting was dissolved.

TB: What did they do?

KC: They started yelling at the government officials. The pandemonium disrupted the meeting. I had also collected a large amount of literature with the idea to write a book. After this experience, I felt the subject was too emotional to deal with.

TB: Tell us more about your work with marijuana.

KC: When in Turkey, I interviewed 13 hashish smokers. Twelve of them said that they would be terribly unhappy if a son of theirs became a user. Clinicians, on the other hand, had a different view. They felt the issue to be a societal one and not a medical one. In the 1970s, I wrote articles about drug dependency and drug abuse. I felt that the control of drug abuse should not be exclusively with the judicial system, because control without rehabilitation would be futile. The health care community should have active participation in the rehabilitation of the chemically dependent.

TB: So, you did a lot of reading on the subject, interviewed users and those who treated the users.

KC: Exactly. There was a professor in Athens, Dr. M. Strigaris, who had written a monograph on hashish. This physician was a student of Professor Lewin, in Heidelberg, who had written a monograph on mescaline. Professor Lewin had encouraged Dr. Strigaris, a psychiatrist from Greece to study hashish. When I went to Greece, in 1966, I visited with Dr. Strigaris. He gave me his monograph and I had an extensive discussion about his clinical experience. In Greece, the prevailing opinion was that the user was going to decline psychologically.

In Greece, in the 1960s, there was a rediscovery of folk music, the boozooki music, otherwise known as rebetico. Musicians of this genre used to smoke marijuana and hashish. A famous boozooki player, Vassilis Tsitsanis, used to smoke marijuana and I went to interview him. His personality was intact and his musical skills were undiminished.

Professor Gerald Caplan of Harvard University had a grant from NIMH to train psychiatrists in Community Psychiatry. He was using a systems approach for mental health consultation. I joined the class from 1968 to 1971. I enjoyed this fellowship and I believed there was going to be a future in Community Psychiatry in the United States.

TB: When did you return to Baylor?

KC: In 1972, I was invited to return to Baylor, and was asked to be the Director of Community Psychiatry in the Department of Psychiatry. Shortly before I got to Baylor, two of my colleagues had died. One was Dr. Moody Bettis, the head of Community Psychiatry. There was another program at Baylor in need of leadership. The Department of Transportation was giving grants to several universities in the United States, some grants to study engineering aspects of vehicular deaths and others to study the effects of alcohol on drivers. My friend and colleague, Dr. John Finch, had applied for a grant to study the behavioral effects of alcohol on driving, DWI offenders, and rehabilitative initiatives that would help to separate drinking from driving. Unfortunately, Dr. Finch and his family perished in a fire in New Orleans inside an elevator of a hotel. When I got to Baylor, I was asked to direct this particular grant. As it was a large grant, I had to recruit several persons. According to protocol, I tried to create relationships with important community resources, such as the probation department and the DA's office. I developed diagnostic facilities for rehabilitation. The project did not receive the attention of the judicial system we were hoping for. A typical DWI offender would get a probated sentence without the judges sending them for rehabilitation. The defense lawyers did not support the idea of any conditions as part of probation.

We tried to persuade the judges, separately, with no success. It became clear to me that “law and order” is not the avenue for the control of drug abuse. We found that DWI offenders were mostly not social drinkers. We found that fifty-seven percent of them were alcoholics and would repeat the offenses many times because of alcohol dependence. With this knowledge and several good professionals, as part of the grant, we did some studies to find the best tests for early diagnosis of alcoholism in the general population. I decided to locate one of the early clinical inpatient programs for the rehabilitation of alcoholics in a large general hospital. Despite some early resistance, this program thrived and became a valuable teaching experience for students and residents.

At Baylor, I also started an anxiety-depression clinic for outpatient studies. In 1973, I received a grant from NIMH to study cyclic nucleotides in the brain after alcohol and morphine administration in animals. With my associate, Bill Askew, PhD, we generated several publications, one of them in the *Journal of Pharmacology and Experimental Therapeutics*.

TB: Didn't you become Chairman of a department in Texas?

KC: In 1978, I became Chairman of the Department of Psychiatry at Texas Tech, a new medical school. I tried to develop a modern department of psychiatry and I stayed there as the Chairman for two years. After attending a number of seminars in medical economics, I became aware that the practice of medicine, in general, and psychiatry, in particular, was to be changed radically. I decided then to return to Houston. It was 1980, when I went to full time private practice. I also assumed the position as director of an acute admissions center for individuals who had severe psychiatric problems. They had to be evaluated and likely committed to a state facility. When I visited that center, I found that patients sent there would be left for two whole weeks without any kind of treatment, during which time they would regress to the extent that the center would look medieval. I had been exposed to something I read in medical literature and saw when I had visited psychiatric hospitals in southern European back in the 1950s and 1960s. I inquired from the legal services of the State Department of Mental Health whether it would be permissible to give the patients medicines without delay. The answer was no. No medications could be given because these patients were there involuntarily. The judge had to see them first and decide about their disposition. The legal services department added that in an emergency, it was permissible to give medication. I started evaluating the patients, carefully assessing their clinical status. After

assessing their status as emergencies, I started prescribing antipsychotic medications and the facility was transformed. The staff started group therapy and art therapy, and many of these individuals did not have to be committed any longer. The administration of medication would permit them to go home. I organized, in Texas, a society for psychiatric administrators, hoping to help forestall the consequences of managed care. With managed care, the stigma of mental illness has returned. In that regard, we have regressed. On the other hand, we now find greater collaboration between neurology and psychiatry. In my clinical practice, I found that it was good to thoroughly evaluate my patients, together with input from internal medicine and neurology. Recently, I decided to quit practice and do only some teaching in psychopathology and psychopharmacology. I also supervise residents at the Medical School of the University of Texas in Houston. I decided to study as well the history of psychiatry in Texas. Many of the individuals, who started the psychiatric societies in Houston, in 1954, and at the state level, have died.

TB: When did Kinross-Wright die?

KC: Dr. Kinross-Wright died in October 1999. Many psychiatrists, who had studied with Dr. Titus Harris when he was the Chairman of Psychiatry at Galveston, have died by now. In 1954, Titus Harris organized the first symposium in psychopharmacology for the American Psychiatric Association. Dr. Kinross-Wright was the main speaker.

TB: When you say history of psychiatry in Texas, do you mean history of psychopharmacology?

KC: I was talking essentially about psychopharmacology. Psychopharmacology in Texas started with Dr. Kinross-Wright. Progressively, the emphasis changed by stressing aftercare, and the comprehensive treatment of drug dependence.

TB: You probably had many associates. Would you name a few of them?

KC: Yes, in my research, I had some excellent collaborators, like Wayne Tansey, Bill Askew, P.C. Johnson, T.J. Skinner, W.K. Huber, A.H. Vogt, A. Hug, L.E. Walker, S.A. Brown, M.L. Clark, and B.J. Zung. I had the good fortune that several of my residents choose psychopharmacology as their elective. A few of them became academic psychiatrists, e.g., Chris Sermas, George Keepers, and George Freemesser. Other associates became interested in alcohol rehabilitation. When I was at Texas Tech, I had several individuals who were interested in drug rehabilitation but I had no program. After we started a chemical dependency program, we trained outstanding counselors. A few of them came from the ministry. Some of them were priests, who had left the church, but had

a great interest in the treatment and rehabilitation of patients. I am convinced that my choice of psychiatry and research in psychopharmacology was a very good choice. In the beginning, colleagues involved in psychoanalysis were somewhat resistant of our initiatives in psychopharmacology. The departments where I was, like Southwestern in Dallas, and Baylor in Houston, have developed productive centers in neuroscience.

TB: You contributed, to many areas of the field. What would you consider your most important contribution?

KC: Both basic research and clinical research are necessary for psychiatry. Additionally, in order to give comprehensive and continuous care, you have to collaborate. You have to bring in many other colleagues from other mental health fields. That is something I learned from Dr. Jolly West in Oklahoma. I felt, on occasion, that I lost some time by studying Community Psychiatry, but in terms of the importance to patients, I feel very happy that I developed a number of clinical centers and aftercare clinics.

TB: So, you consider one of your important contributions to the field is the establishment of centers for clinical and basic research.

KC: Yes, because the question is how to apply research findings to patient care. Dr. Kinross Wright had many good initiatives. For instance, he had started a large center in the prison system. When Dr. Frazier followed him, we developed relationships with the state hospitals. Later on, I revamped the unit for the criminally insane and tried to introduce more diligent work in assessing and documenting psychopathology, creating a clinical chart. The mental health system has decreased in its scope and incarceration has exploded. Seventy percent of those individuals are there for drug abuse and very little rehabilitation is taking place. I feel that mental health and psychiatry should be given a greater priority in public health. The ideas of Professor Gerald Caplan, in Community Psychiatry need to be applied.

TB: Do you think that those centers you established could play an important role in the community?

KC: Yes, because the centers proved themselves. The centers became very popular among the public. The clinic I started in Houston became so big that it took over the Psychiatric Institute and compromised research. As a result, the Institute was taken from the state psychiatric system and given back to the psychiatric department of a medical school. I feel that a balance has to exist in

academic medicine and in psychiatry, between clinical work and research. You cannot teach psychiatry in theory only. I think one of the things that I learned from great physicians like Michael DeBakey and Denton Cooley is that research has to move concurrently with clinical excellence. I felt that I was very lucky to have professors of that caliber in medical school.

TB: Am I correct that you said that your current activities are restricted to teaching?

KC: Yes.

TB: So you have retired from your other activities?

KC: I retired from clinical practice.

TB: When?

KC: Very recently.

TB: You have been teaching all through your professional life. Have you been teaching also in departments outside of psychiatry?

KC: Other departments in medical school do not want psychiatrists in their teaching programs. They want psychologists. We have this competition between psychologists and psychiatrists.

TB: Do you feel very strongly that psychiatrists should do the teaching?

KC: Very much so.

TB: Were you teaching primarily psychopharmacology and psychopathology?

KC: Psychopathology, community psychiatry, and psychopharmacology.

TB: So, you feel your greatest contribution was that you implemented a comprehensive system for psychiatric services in Texas?

KC: Yes. As we know, the American society is changing. We have very many immigrants. We have people who really have difficulty in communicating. We have individuals with problems of self-esteem. We have difficulties in education, and people have problems in planning their future. The role of psychiatry is not simply to deal with symptoms, but to assist in personality development and life planning.

TB: You are a member of many societies. When did you become a member of the ACNP?

KC: I submitted my application in 1964, and I became a member in 1965. I became a member of CINP more recently. I have been a member of The Society of Neuroscience and of Biological Psychiatry from the 1960s.

TB: Did you serve on committees in these societies?

KC: I served on many committees, but mostly at the state level, in administrative committees and planning committees. Recently, I received the award for “Excellence in Psychiatry” by The Texas Psychiatric Society. I served on committees in the Texas Medical Association, the Texas Psychiatric Association, and the APA. I was a member of the state mental health board for eight years. For four years, I was the chairman.

TB: You have also published many papers?

KC: Yes.

TB: One of the early papers you mentioned was published on a long-acting phenothiazine preparation. Would you like to talk about that?

KC: Yes. I feel the long acting preparations help the patients with compliance. When Squibb developed fluphenazine enanthate, the first long acting medication, the company did not market it well. However, when other long acting preparations came along, the distribution and use of long-acting preparations improved.

TB: Is there anything you would like to add?

KC: I want to express my gratitude to this society, the American College of Neuropsychopharmacology, for promoting balance between basic and clinical research. When I was taking my boards, in 1965, I had to take exams in basic and clinical neurology. One third of the exam was in neurology and I really enjoyed whatever knowledge I had learned. It seems now that neurology is coming back. It took practically fifty years for neuroscience to become involved.

TB: Well, thank you very much. Hope you will continue teaching for many years to come.

KC: Thank you very much.

10. THOMAS N. CHASE

TB: This will be an interview with Dr. Thomas Chase¹² for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College, in San Juan. It is December 7, 2003. I am Thomas Ban. Let us start at the beginning; where and when were you born? Could you say something about your education?

TC: I was born in a small town near New York City called Westfield, NJ, in 1932. My family consisted mostly of lawyers and business or financial people. Not a single one was an academician, a physician, or a scientist. So I had no real background in those fields. Early on, I became interested in how things worked and I would love to take apart mechanical and electrical gadgets. I was particularly fascinated by radio receivers and transmitters, and later by television. I became an amateur radio operator and maintained an interest in electronics as I grew older. When it came time to decide what I wanted to do for an education, my family declared that I would go into business and start with an engineering degree. In those days, around 1950, children pretty much obeyed their parents. So I said, OK, and since I liked things electrical, I chose to train as an electrical engineer. Then I had to decide where to go to college. That turned out to be rather easy when my girlfriend selected Wellesley. The only engineering school in the Boston area that I knew about was MIT. And so, that's where I applied. Fortunately, they acted on recommendations from my high school principal and a prominent local alumnus, so I was spared the risk of taking examinations. During the first few years at MIT, I became interested in potential engineering applications to medicine, and particularly, in how circuits worked in the brain and whether one could apply electrical engineering principles to the understanding of central nervous system function. I devoted my college thesis to how, what was then called cybernetics or feedback theory, might relate to cognitive processing. Studies of human cognitive functioning have continued to fascinate me.

¹² Thomas N. Chase was born in Westfield, New Jersey in 1932. After an electrical engineering degree from the Massachusetts Institute of Technology, he worked as an engineer and served in the Korean War. He received his M.D. degree from Yale University and completed neurology training at the Massachusetts General Hospital in Boston. He subsequently went to the National Institutes of Health in Bethesda MD, where he occupied various positions in the Intramural Research Programs of National Institute on Mental Health and the National Institute of Neurological Disease and Stroke. He was interviewed in San Juan, Puerto Rico on December 7, 2003.

TB: Are we in the early 1950s?

TC: This was around 1953 and 1954. I wondered about how people communicated with each other and how brain neurons transferred information through its neural networks. As these thoughts progressed, it became clearer that I didn't really want to do ordinary engineering, but rather the biological applications of engineering. Nevertheless, after graduation from MIT, I felt obligated to return to the Singer Sewing Machine Company, where I had worked during summer vacations, and which, at that time, employed some 75,000 people around the world. My experience at Singer was informative, since it reinforced my evolving thoughts about not pursuing a standard engineering career. I was assigned various projects, like improving the delivery of lubricants to the gears of a sewing machine, which were not very challenging. I was also disappointed to find out how this once great company functioned in terms of product development. For example, they designed the mechanical process by which cloth is stitched together purely empirically. The company had no clear understanding about how the thread tensioning system and the coming surface of the shuttle actually worked to form a stitch. They simply gave a block of steel to a toolmaker and asked that he file it so that it throws off the thread in a way that the hook catches it and makes a knot that neither sags nor puckers. I was disillusioned and wondered why I should spend my life with a company that seemed to have so little interest in what it was doing. When I asked about how Singer went about updating their products, an official took me to a room where sewing machine parts were laid out on tables. All these components came from competitors. It was appalling to realize that the Singer approach to improving their machines relied mainly on copying their competitors. Finally, let me tell you about one other disillusioning experience I had with the Singer Company. I lived at a men's club in Bridgeport, CT, and one of the other residents during much of the workweek was a man, who served as the Singer vice-president for research and development. We often had dinner together and from these encounters, I learned a lot about the issues of greatest concern to the company's upper management. To my dismay, I found out that one of the major problems at the time was to decide whether sewing machines should be painted brown or green. How sad, I thought, to have such a smart and successful engineer end up having to bother with such trivial matters. I knew that this was not the direction I wanted to go and began to look for a way out.

The army rescued me. I had been an ROTC student at MIT and upon graduation, I was commissioned a second lieutenant in the Signal Corps. After completing military training in New Jersey, I was shipped off to the Korean War zone, where I took command of a platoon responsible for maintaining telephone communications between the country's airports. This assignment proved to be a challenging and sometimes alarming experience. When I joined the platoon, I discovered that much of its equipment was missing. When I asked the senior supply sergeant why, he said the platoon had been overrun in battle, many of the troops were injured or killed, and most of the equipment was lost. So here I was, a naïve young man from small-town America, suddenly confronted with the awesome consequences of war. An armistice had been signed and organized fighting had ceased. But the devastating consequences of war were everywhere. It's with unending sadness that I now recall the awful plight of the civilians around us. The battalion, to which I was assigned, occupied portions of a small village south of Seoul. The village consisted mainly of rice paddies, surrounded by small thatched houses and a bombed-out textile mill. The troops lived in Quonset huts, but the officer's quarters were set up in a section of the mill. Although mostly in ruins, it was still the nicest place in town. Detachments of my platoon were spread across the county, near the various airfields. Thus my job allowed me to travel the length and breadth of the land. The main inter-airbase communications system depended on copper wires strung on telephone poles. That turned out to be a big problem. Landline communications relied on a commodity of compelling commercial interest to the impoverished people surrounding us. So we played an interesting game. Each day my linemen would string new wires and each night the locals would take them down. As you can imagine, it was a rather hectic life.

Several informative experiences during my time in Korea remain etched in memory. First, I made friends with two Korean high school students. The deal was that on weekends, I would drive them anywhere in my jeep, if they would choose interesting places and serve as informed tour guides. They did, and I learned a lot about their culture and how different civilizations approach similar problems. To this day, I maintain contact with both men, who went on to highly successful adult lives. A second experience concerned techniques to inspire others to do what needs to get done. The work of our platoon was basically tough and dangerous. Most serving in Korea were not there by choice but had been drafted into military service. Getting soldiers to perform well in such a demanding situation is challenging. Military discipline helps, but it's not

enough. The situation forced me to learn how to be a better leader and the lessons learned have helped ever since. Finally, while in Korea I had time to think about what I should do with the rest of my life.

Having decided that a business-engineering career was not for me, what else could I do? My thoughts returned to an early fascination about finding out how things worked. This interest began to focus on nervous system function, while choosing a topic for my undergraduate thesis. Now I began to read medical books and show myself medical training films, not a difficult task, since one of my responsibilities was to supervise the movie depot for our troops in Korea. I also had an opportunity to work in a nearby Leper colony, which gave me a glimpse into what the practice of medicine was like in such a needy group of individuals. By the time my term of military service was over, I had firmly resolved to go back to school and become a doctor. Going back to tell my father of this decision was a little rough. He sort of shook his head, saying you can't make money off sick people. Impetuously, I fired back that I didn't intend to charge any sick person for providing medical care. And to this day I have kept that promise. My father eventually struck a deal with me. He offered a small allowance, I don't even remember what it was, but otherwise I was on my own. Getting married helped solve the financial problem. But dealing with the emotional problem of having little family support was harder. Often during those initial years, I wondered about the wisdom of my decision. Now, in retrospect, I can tell you I made no mistake. I made a choice that was exactly right for me. And ultimately, my family seemed proud to see me graduate from medical school and pursue a career in neurosciences research. To get ready to apply to medical school proved to be a bigger challenge than I had expected. I had taken none of the traditional premedical courses and began attending night school at Columbia University to fill in the gaps. I was officially labeled an "atypical applicant" by the Columbia premedical program, which alarmed me and made me realize the whole venture could end badly. But the schoolwork proved easy and I got good enough grades to essentially pick my own medical school. The maturity gained since college also helped. I recall one rather hostile medical school interviewer, who seemed to enjoy asking rather demeaning questions. At one point, he asked whether I had chosen to be a doctor to get rich. Fortunately, it was my practice to spend time in the school library at each place I interviewed. And so, I knew about what this young instructor of surgery was earning. It was less than I had been paid at Singer. When I put out my hand and asked whether he was willing

to bet that I'd already earned more than he did, the interview suddenly turned rather collegial, and in due course, I was accepted at that school for admission. But my interview with the Dean at Columbia Medical School was the most memorable. I had read about Dean Rappleye and knew that he had enjoyed a distinguished career in medical education. He was a large and imposing man, ensconced in an impressive office. I approached him anxiously. Since this was my school of choice, I asked why he bothered to see me, since Columbia was well known to accept only typical applicants from the top of their class. A gracious and perceptive man, he answered by reviewing what I had done in college in a most complementary way. He particularly liked my interest in applying engineering principles to medical problems. My confidence was restored, and we began a lengthy and wonderful conversation. At one point, I kidded him about his school's strict dress code. All Columbia medical students wore identical, immaculately starched, white coats, and looked like they came from the same cookie cutter. There followed an engaging discussion about uniformity versus individuality in medical education. Several years later, an acquaintance, an Assistant Dean at Columbia, told me that Rappleye spoke to others about how impressed he had been by our conversation. I, too, was excited by our encounter, but that didn't convince me about the merits of conformity. For that reason, and others, I chose to go to Yale, rather than Columbia. Yale seemed to have a uniquely mature attitude towards medical education. The school assumed that anyone they admitted would take responsibility to learn the basic material. No class attendance or exams were mandated. And plenty of time was left for individual study and research. Upon entering Yale, I assumed I would gravitate towards neurology and the neurosciences. But it didn't take long before I realized that my original ideas about using engineering principles to solve neurological problems were hopelessly naive. I did a little lab work with two neurophysiology investigators but found their research to be uninspiring. So, I ended up trying to apply some engineering approaches to a study of protein cross-linking in relation to arterial elasticity and blood pressure regulation. Unfortunately, the mentor I chose was a cardiac surgeon, interested in pumps, but not in the problem I wanted to study. It was just as well because the work never amounted to much. But it did expose me to the thrill of laboratory research and I was forever hooked. I also came to the realization that primarily seeing patients might not be all that satisfying. While the practice of retail medicine held many attractions, I thought wholesale medicine might be better for me. I thought I'd rather spend my life trying to figure out how to improve the practice of medicine,

rather than just applying what was already known. So I decided by the end of medical school that I really did want to go into neurology, both from a clinical and research point of view, and to focus on pharmacology and experimental therapeutics. In the mid 1960s, neurology strongly emphasized diagnostics and had relatively little interest in therapeutics. At the time, “diagnose and adios” was the humorous characterization of neurologists. This attitude seemed a bit defensive, since few effective treatments were available, and prospects for improving that situation seemed daunting. Drugs then available for brain disease had largely been discovered serendipitously. The concept of trying to figure out how the nervous system worked, how disease altered normal function, and on that basis developing a rational intervention was not seriously discussed. The Chair of Internal Medicine at Yale was Paul Beeson, one of the all-time greats of his profession. I was a medical student in his department and served under him as a medical intern. During these periods, he influenced me in many important ways. Not the least of these was his advice to go to Harvard and the Massachusetts General Hospital for neurology residency training. He said during our last meeting, while handing me his autographed textbook of medicine, that he had written his very best reference letter, and now it was up to me. Looking at the other top neurology residencies at the time convinced me that he was right. So I moved to Boston and started work at the Mass General. The clinical part was demanding but made entirely worthwhile because of Raymond Adams. In retrospect, I would certainly place him as the most distinguished neurologist of this time. Encyclopedic in his knowledge and logical in his reasoning, he was always kindly and discerning in his approach to others. He quickly understood his patients and his students. He allowed me time to explore the rapidly emerging world of neuroscience at Harvard Medical School. At the end of my clinical training, I told him that I thought I had some beginnings of understanding about what the practice of neurology was all about, but that I really didn’t want to go in that direction. Caring for neurologic patients was a source of great personal satisfaction, but I wanted primarily to devote myself to research in neurotherapeutics. To my surprise, since he was a neuropathologist and rarely spoke much about therapeutics, he became very interested. He said my plan was right for me and suggested that I go to NIH and spend some time learning to do research, and then come back to Boston. He advised me to see either Sidney Udenfriend or Seymour Kety. I went to Kety. He had come to Harvard to give a lecture during my residency that impressed me enormously. Up to that point, it seemed most neurologic researchers were simply

measuring things, whatever their assays allowed, and then looking for correlations between their measurements and various clinical attributes. Today, we would call these plodding efforts fishing expeditions. Kety took a much more scientific, hypothesis testing approach. He showed how it might be possible to study linkages between specific brain dysfunctions and particular clinical symptoms, using chemical and pharmacologic techniques. He illustrated this possibility by describing how abnormalities in certain neurotransmitters might relate to depression. It seemed like a generalizable concept. And it related directly to therapeutics, since drugs might be designed to selectively correct either too much or too little transmission in a particular system. When I met Kety, he expanded on these ideas, and suggested I discuss them with others in his group, especially Julie Axelrod and Irv Kopin. By day's end, I was excited about the potential of what was then called transmitter pharmacology and had decided to join Kopin's lab. I started working on animal experiments, but with an eye towards clinical applications. It was an amazing time, since there were so many smart people around from whom I could learn. This was NIMH, and most in Kety's group were focused on the problem of depression and to a lesser extent on schizophrenia. But, of course, my inspiration came from neurology. I was particularly interested in transmitters in the basal ganglia and how they might relate to parkinsonian symptoms. At the time, Arvid Carlsson was beginning to publish his classical papers on dopamine and serotonin and motor function. The discovery of levodopa for Parkinson's disease by George Cotzias also occurred during my training at NIMH. Clearly, the opportunities to apply transmitter pharmacology to neurologic disease were wide open and NIH seemed like the ideal place to take advantage of these opportunities. It amuses me today to think about the simple administrative procedures that sufficed to gain NIH tenure, in the 1960s. One day, just two years after beginning my postdoctoral training, the NIMH administrative officer approached me in the lab and asked whether I would like to become a regular government employee. I was then paid by an NIH fellowship that still had another year or two before expiring. The last thing I was thinking about was finding a job. My initial reaction was that I didn't want to become a civil servant and would eventually prefer an academic appointment, especially the one promised at Harvard. But Hazel Rhea was an imposing woman, not used to taking no for an answer. She told me that accepting a government appointment would increase my salary, and that I could resign on just two weeks' notice. So I soon became a permanent NIH employee, with none of the paperwork or committee reviews that so encumber the tenuring process

today. Interestingly, I maintained contact with my former bosses at the Mass General, and they initially implied that when I came back, it would be at the instructor level and without tenure. The next time this matter came up, they said when you come back, you'll be an assistant professor. Soon I caught on that because I was spending full time doing research and publishing a lot, I was advancing faster in the Harvard system than I would have if I had actually stayed there. The work at NIH was exciting and I decided to remain for the time being. Thirty-five years have now flown by and I've yet to regret that decision.

TB: Could you tell us about your activities at NIH?

TC: By all usual standards, my career was upside down. My research went well, and two years after accepting tenure, I was promoted to the level of Section Chief. In that position, I was assigned a lab technician and a part time secretary. I spent my time doing clinical research using several assigned beds and related pharmacologic studies in a nearby one-room lab. Then two years later, in 1974, as my own independent research was just beginning to pick up some steam, I was unexpectedly called to Don Tower's office and told that I had been selected to serve as the Scientific Director of the National Institute of Neurological Disorders and Stroke (NINDS). He explained that I would take responsibility for all the Institute's intramural research efforts, as well as a number of off-site projects. I had little idea about what scientific directors did, and the thought of having 600 scientists and support people reporting to me, most far more senior than I, seemed a bit overwhelming. But the prospect of taking charge of what was then the country's biggest neuroscience program was irresistible. Spending full time on my own research would have to wait. The mid-1970s were a great time to be at NIH. Resources were plentiful. Scientific productivity and prestige were at their peak. The bureaucratic superstructure was still lean and committed to promoting the scientific enterprise, not the other way around. NIH attracted the best and brightest young scientists, although it must be conceded that this was partially due to the fact that many sought to avoid the military draft by working at a Federal institution. Among the senior staff, many were world leaders in their fields. Excitement and morale ran high and prestigious prizes and other forms of professional recognition came frequently. Members of the National Academy of Science were everywhere. An NIH intramural researcher received a Nobel Prize nearly every other year during that period.

TB: Was the Nobel laureate who worked in your group at that time Gajdusek, or Axelrod?

TC: Carleton Gajdusek was the one in my group. He received the prize, in 1976, for work on Kuru, a spongiform encephalopathy due to prions. Just a few years before, soon after my period of working with him, Julie Axelrod had also won a Nobel Prize. His prize, as you know, was for studies on synaptic transmission mediated by catecholamines. Many of the approaches he took seemed directly applicable to studies of dopamine and Parkinson's disease, as well as to other neurologic disorders, where pharmacologic manipulation of synaptic mechanisms might be a rational approach to therapy. He also taught me, like so many others in contact with him, if you can't prove your hypothesis in a four-rat experiment, then it's probably not biologically worth pursuing. Julie and Irv had a big influence on the directions I wanted my own research to take, when I transferred to NINDS, and began to organize a neuropharmacology laboratory. At the start of my tenure as the NINDS director of intramural research, I had a number of short and long-term goals. At the top of my list was a commitment to launch an experimental therapeutics program. I felt that clinical neurology was seriously behind in this area and that the NIH offered an ideal environment for this work to flourish. But before expanding on this, let me mention a few other initiatives that I now recall with special pride. Overriding, was the opportunity to recruit outstanding young scientists and begin new research programs. One of these involved brain imaging, which when I started the NIH effort, involved just positron emission tomography (PET) scanning. Early on, it served as a model for establishing extramural PET centers across the country. Another was to organize an international effort to standardize brain banking. NIMH helped with this work, which involved getting the neurosciences community to establish standards for collecting and assaying CNS tissues, so that human post mortem findings from one lab could be reliably compared with others. I also had the opportunity to begin or rejuvenate NINDS research operations at the Marine Biological Laboratory (MBL), in Woods Hole and on Guam, where pioneering studies on the local forms of Parkinson's disease and amyotrophic lateral sclerosis (ALS) had been conducted. A decade later, when I had stepped down from the Scientific Director's job, the NINDS intramural program had doubled in size and in citations to its publications. There are so many other things that I should mention about this, but before time runs out, let me return to my interest in neurotherapeutics. My goal upon joining NINDS was to organize a lab that was vertically integrated. By this, I mean a research group that attacked the same general problem with various technologies and at various levels from the basic to the clinically applied. The NIH

structure was well suited to this concept, since the 526 research beds at the Clinical Center were surrounded by related lab facilities. Geographic proximity facilitated the efficient transfer of ideas and materials from bench to bedside and back again. Some research problems are best begun at the clinical level. Others lend themselves more to experiments at the molecular or cellular or whole animal levels. I started a lab that spanned the entire spectrum but focused on the medical needs of patients with neurodegenerative disease. Today this approach is no longer uncommon. Now, it's called translational research. While my interest in amine pharmacology derived from my experiences with Kopin and Axelrod, my attraction to Parkinson's disease began much earlier. During residency training, I had been affected by the plight of parkinsonian patients and those with similar movement disorders. I was impressed that they had a rational treatment, the anticholinergics, even if the effect size was small. One of my most memorable teachers at the Mass General was Bob Schwab. He was full of interesting ideas about the pharmacotherapy of movement disorders. He had done pioneering work with apomorphine and with amantadine. And he was also among the first to develop a scale to quantify motor disability in Parkinson disease. So Schwab had a big influence on my choice of career directions. At the time my NINDS lab was beginning, following close upon the classical preclinical studies of Carlsson, George Cotzias discovered how to turn the earlier observations of Birkmayer and Hornykiewicz into a practical and effective treatment for Parkinson's disease. Immediately, the race was on to extend and perfect the concept of transmitter replacement in neurologic disease. For Parkinson's disease, the big problem was that levodopa did not replace the depleted neurotransmitter, dopamine, in a very physiologic way. For that reason, patients who did well initially, eventually began to lose benefit and develop a syndrome, called motor response complications. A disabling hypokinesia was replaced by an equally disabling hyperkinesia and other motor abnormalities. Early on, most working in the field attributed motor complications to pharmacokinetic issues. Before long, however, it became clear to me that pharmacokinetics could not explain the entirety of this problem. Another popular view, even to this day, has been that motor complications reflect denervation supersensitivity of postsynaptic dopamine receptors, even though the data give scant support for this simplistic idea. My thought was that the periodic administration of levodopa only restored striatal dopaminergic transmission, episodically. But the nigrostriatal dopaminergic pathway functions largely as a tonically, not phasically, active system. And so began a line of

research that I have pursued to this day. I wanted to figure out whether my hypothesis that the nonphysiologic stimulation of the nigrostriatal dopaminergic system was responsible for the motoric adverse effects of levodopa therapy, and if so, what were the consequences at the neuronal level, as well as in downstream networks, and how could we give dopaminergic treatments in a more physiologic, and thus, less detrimental way. I felt the answers to these questions might have relevance to other transmitter systems and other brain disorders, including those where therapy might involve the inhibition of synaptic transmission. Some of our earliest studies involved the continuous parenteral infusion of dopaminomimetic drugs to parkinsonian patients. Since the dopamine system fires off fairly constantly, at about five Hertz, and since, as a first approximation, the amount of dopamine released into the striatum is a function of the rate of nerve impulse activity, it follows that the amount of the transmitter in contact with its postsynaptic receptors normally remains quite stable. On the other hand, treating a parkinsonian patient with levodopa produces marked fluctuations in striatal dopamine. With each oral dose, dopamine levels shoot far above the physiologic range and then soon fall back to sub-physiologic concentrations, since both extracellular levodopa and dopamine are rapidly metabolized. So, with standard therapy, you're chronically pulsing a neuronal system that normally functions continuously. To test our hypothesis and determine whether continuous transmitter replacement might prevent or reverse the motor complications syndrome, we gave patients constant infusions of levodopa or dopamine agonists for days or even weeks. It worked. Motor complications abated. And in primate models of Parkinson's disease, we later found that initiating treatment with continuously administered agonists actually prevented onset of these complications. So now, I was sure that motor complications were a consequence of chronic nonphysiologic stimulation.

TB: In looking for effective treatments did you work with the pharmaceutical industry?

TC: Early on, we established a close working relationship with Merck. Nowadays, NIH regards such collaboration between government and industry with suspicion, and the easy opportunities to hasten clinical development of innovative products by joint efforts of this type have largely disappeared. Merck was trying to develop levodopa formulations that reduced GI intolerance and improved convenience by prolonging their duration of action. The company seemed most concerned about their patent and marketing position. Our interests lay in finding better approaches to therapy and in evaluating the continuous versus intermittent stimulation hypothesis, which then

was little known or understood beyond our lab. The first levodopa improvement involved the addition of a dopa decarboxylase inhibitor, which we found reduced the initial nausea and vomiting, and thus, allowed a far more rapid dose titration. But it didn't significantly prolong levodopa's duration of action. And neither did the next upgrade, the various controlled release formulations, which we also contributed to in major ways. Both levodopa improvements were clinically useful and led to a product that remains the gold standard for the treatment of Parkinson's disease. Both helped patients, although not because they reduced the problem of intermittent dopaminergic stimulation and resultant motor complications. The search for pharmaceutical strategies to deal with that problem, including the development of longer acting dopaminomimetics, continued for many years. Progress was slow, and my lab made relatively few contributions. My duties as Scientific Director prevented spending much time on my own research, which in any event, had now turned in other directions to avoid competing with my newly recruited Clinical Director, Don Calne, an internationally recognized expert on Parkinson's disease. Eventually, several dopamine agonists with very long half-lives were discovered by industry. Other approaches to more continuous dopamine system stimulation that my lab subsequently worked on, that ameliorated this problem, included miniature wearable pumps, subcutaneously implantable polymers and skin patches. We launched the initial proof of concept trial for what could be the first transdermal preparation approved for Parkinson's disease. The tortuous story of its development is interesting since it illustrates the enormous time and effort needed to bring a drug from discovery to market. In the mid-1980s, my search for a dopamine agonist suitable for continuous administration led to Alan Horn's lab at the University of Groningen. He proudly showed me a series of recently discovered aminotetralins that were potent dopamine-D₂ agonists. But an overlooked characteristic of one of these drugs immediately got my attention. It appeared to be highly lipid soluble, and thus, might work as a transdermal preparation. So, I helped arrange its acquisition by a small California company that named it N0437 and began work on formulation. Over the next 10 years, the drug struggled through 4 or 5 under-funded and under-skilled companies in several countries before being finally ready to try as a patch in humans. We found that it successfully reduced response fluctuations, and the preparation should soon be approved for marketing as rotigotine. Neurologists initially tended to be skeptical about our intermittent versus continuous stimulation story. Thus, I'm pleased that the newer long-acting agonists have been

shown to significantly delay onset of motor complications in patients, just as we had earlier predicted, based on studies in animal models. And now patch technology also appears to be on the verge of clinical utility. Clearly, the trend towards more continuous dopaminergic replacement has benefited all those suffering from Parkinson's disease.

TB: In addition to helping patients, how did your work illuminate mechanism of action?

TC: I'd like to say something about the pathophysiology of the motor complication syndrome and how fundamental studies of these mechanisms have enhanced our understanding of CNS function. In the late 1970s, we began to look at the role of GABA and glutamate mediated functions in the basal ganglia, and how these transmitter systems influence motor function. Some of our earliest studies looked at the relation of these striatal systems to the motor dysfunction in tardive dyskinesia. But soon, our efforts returned to the Parkinson's disease problem and began to focus on the medium spiny neuron. These remarkable cells make up the vast majority of striatal neurons. They express both D₁ and D₂ dopamine receptors and receive input from the substantia nigra. They also express glutamate receptors and receive input from all areas of cerebral cortex. And spiny neurons project directly and indirectly, via gabaminergic terminals, to the major output nuclei of the basal ganglia. Clearly, the medium spiny neuron must be critical to basal ganglia function and we needed to know how this worked. Soon, we discovered that something was happening to the sensitivity of ionotropic glutamate receptors on spiny neurons in response to changes in dopaminergic input. Our studies began to show that both N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor blockers could alter the effects of dopaminergic drugs on motor function. Slowly, the details of these interactions emerged from our work in rodent models. Since various forms of neuronal plasticity were mediated by glutamate transmission via the NMDA receptor, we examined the effect of MK-801 (dizocilpine) and other NMDA receptor blockers on the development of motor complications during chronic treatment of parkinsonian rats with dopamine agonists. Tom Engber and others in the lab found that pretreatment with MK-801 both prevented and reversed the motor dysfunction mimicking motor complications in parkinsonian patients. These results were later confirmed by Stella Papa in the primate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease. Finally, as the culmination of all this step by step work, we launched a clinical trial of amantadine, then the only NMDA antagonist available for human use, in patients with intractable

motor complications. In 1998, Leo Verhagen Metman and others reported that amantadine significantly improved levodopa induced dyskinesias and motor fluctuations. Amantadine remains today the standard pharmacotherapy for motor complications, even though it's long off patent, and has never been promoted by any drug company. The results of our small, yet well-controlled trial, since replicated by many other groups, had a major impact on the lives of those with advanced Parkinson's disease.

TB: This seems like an excellent example of what you referred to earlier as translational research.

TC: It is. The discovery that amantadine benefits parkinsonian patients with response complications was particularly important to me, because it reinforced my view that truly novel treatments can be found by small groups through the painstaking application of fundamental scientific principles. We started with insights at the molecular level and proceeded to evaluations in rat and non-human primate models, and then finally, in man. The basic idea arose from our observation that dopaminergic input to spiny neurons affected the sensitivity of coexpressed glutamatergic receptors. This led to studies of the bidirectional signaling between D1 and D2 dopaminergic receptors and ionotropic glutamatergic receptors. We found that the nonphysiologic stimulation of dopamine receptors altered the phosphorylation state and channel characteristics of nearby NMDA and AMPA receptors. These changes reflected the aberrant activation of kinases or deactivation of phosphatases that control the amount of phosphorylation at particular sites along the intracytoplasmic tails of these glutamatergic receptors. The receptor alterations increased their sensitivity to cortical excitatory drive. As a result, striatal output evidently changes in ways that favor the appearance of parkinsonian signs and response complications. Clinically, we now know that although other NMDA antagonists attenuate the motor complication syndrome, those that are non-selective for all NMDA receptor subtypes are not very useful. So our attention turned to drugs that target the NR2B subtype of NMDA receptors. These drugs appear to be very effective in our animal models, and clinical trials of NR2B antagonists should begin soon. In addition, we are now finding evidence suggesting that NMDA and AMPA receptor antagonists may have additive effects in rodent and primate models. Perhaps a cocktail of both antagonists would prove safer and more effective than either given alone. Hopefully, a clinical evaluation of this possibility will start in the not too distant future. Our studies thus suggested that sensitization of NMDA and AMPA receptors expressed at the dendritic tips of spiny neurons play a crucial role in the pathogenesis of

motor dysfunction in Parkinson's disease. Since protein phosphorylation serves as an important regulatory mechanism for these receptors, the differential changes in the phosphorylation state of certain tyrosine and serine residues that we found occurring as a result of nigrostriatal system degeneration or intermittent dopaminergic treatment likely contributed to their altered synaptic efficacy. These thoughts raised the possibility that we might be dealing with one aspect of a more general phenomenon. At the time, little was known about signaling in medium spiny neurons or about how these neurons integrate inputs from their various receptors. Extending our observations about how signaling between dopamine and glutamate receptors functioned, we began to look at whether similar mechanisms might be operative at other transmitter receptors expressed on these striatal efferent neurons. If the way one receptor was stimulated regulated the synaptic efficacy of others then, we wondered, could this be a way that neuronal dendrites approach the challenge of synaptic integration? The implications of this concept for the treatment of motor dysfunction seemed obvious. Could blockade of other, nondopaminergic and nonglutamatergic, transmitter receptors expressed on spiny neurons affect motor function and, more specifically, ameliorate symptoms due to a decline in striatal dopaminergic input or chronic exposure to nonphysiologic dopaminergic replacement? If some of the various transmitter receptors expressed on spiny neurons modulated the way cortical glutamatergic input influenced striatal gabaminergic output, then drugs that interact with these receptors might treat motor dysfunction due to disease or treatment related abnormalities involving one of the other receptor systems. To make a long story short, we have been exploring these possibilities in relation to the adenosine A_{2a}, the serotonin 5HT_{2A}, and the α_2 - noradrenergic systems. In each case, it now appears that selective blockade of one of these receptor classes ameliorates Parkinsonism or motor complications or both. These studies were started in rat and then primate models, and we have already started, or we are planning to start, clinical proof of concept trials. These strategies open up an entirely new approach to the treatment of Parkinson's disease, and perhaps other neurologic disorders, as well. Rather than the traditional approach of replacing the deficient transmitter, it may sometimes be safer and more effective to pursue novel pharmacologic strategies that prevent or reverse subsequent reactive changes. In Parkinson's disease, we might no longer be limited to simply replacing dopamine at spiny neurons, but rather have the option of pharmacologically modifying other systems with countervailing actions at these neurons. More generally, we might no longer be constrained to

think only about directly correcting the malfunctioning transmitter system but could consider pharmaceutical interventions that tend to reverse the downstream consequences of the original malfunction.

TB: When did you do this work?

TC: These are experiments mainly carried out over the past five years, although the concepts had been percolating within the lab for a bit longer. What I've been describing are examples of the general concepts that have long guided my research at NIH. I sought to apply and extend what is already known about neural mechanisms, especially interneuronal transmission, and more recently, intraneuronal signaling, to the discovery of better pharmaceuticals for the treatment of brain disease.

TB: You started treatment of Parkinson's disease with anticholinergics. What is their status now?

TC: Before the discovery of levodopa, the anticholinergics were all that was available to treat Parkinson's disease. But they confer only meager benefit to early stage patients and can cause confusion and somnolence. The pharmacology of anticholinergic therapy of Parkinson's disease hasn't really advanced since the 1950s. The drugs we have today are essentially the same as those we had then. Usage is low. Nevertheless, much more has now been learned about CNS cholinergic receptor subtypes and it might be useful to go back and see whether selectively targeting a particular subtype might improve their therapeutic index. It's an area that warrants future attention.

TB: What is the current status of MAO inhibitors in the treatment of Parkinson's disease?

TC: A fair amount of work has been done on monoamine oxidase inhibitors. Drugs of this type have relevance to Parkinson's disease for two reasons. For palliation, MAO inhibitors provide modest symptomatic relief as monotherapy in early stage patients and they may also help a little in smoothing out motor fluctuations in later stage levodopa treated individuals.

TB: Type B inhibitors, or all MAO inhibitors?

TC: Selective inhibitors of the MAO-B isoform are used clinically for safety reasons. The second reason that parkinsonian patients receive drugs of this type is because of their disease modifying potential. Interestingly, there is evidence suggesting that their neuroprotective activity in animal models could reflect mechanisms other than MAO inhibition. But the results of clinical neuroprotective trials have been hard to interpret. A big problem has been in trial design, particularly the lack of outcome measures that accurately reflect the underlying disease state. All

studies, to date, have failed to prove that MAO-B inhibitors are neuroprotective. But, on the other hand, they didn't rule out that possibility. So, the work continues.

TB: In the United States?

TC: In the United States and elsewhere in the world.

TB: In the course of your research did you have any contact with psychiatry?

TC: My first seven years at NIH were spent at NIMH, where I was surrounded by talented psychiatrists and their exciting work in psychopharmacology. My initial lab experiences included sharing a bench with Joe Schildkraut and Saul Schanberg, and later sharing an office with several psychiatrists, including Chris Gillin and Keith Brodie. Biff Bunney's affective disorders group, which then included Fred Goodwin and Dennis Murphy, was nearby. Dick Wyatt got me interested in the relation between monoamines and sleep. John Davis started me to think about psychosis and monoaminergic mechanisms. Interactions with these, and many other individuals, taught me a lot about how to approach the clinical study of brain disease and shaped the directions my future research would take. Like many around me at NIMH, I began to use drugs as tools to selectively manipulate brain transmitters, especially those measurable in spinal fluid, and specific clinical functions, especially motor and cognitive functions. Using this pharmacologic approach, one could infer a great deal about the relation of specific transmitter systems to particular clinical behaviors. Soon, I was attracting others to work with me and was able to begin the first NIH clinical group focused on neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease. Although most who subsequently came to do clinical research in my group were neurologists, I also had the privilege of training a number of psychiatrists, at least three of whom went on to chair their own academic departments, and one who became a president of the ACNP. Just now, I'm preparing for an upcoming NIH celebration for all the young people who have passed through my lab. It was surprising to find out that the total is now somewhere around 120, and to realize how many had already made extraordinary accomplishments and risen to positions of high responsibility in the academic, government and industrial worlds.

TB: Your years at the NIH have shaped both the lives and careers of others and your own.

TC: Due to my experiences at NIMH, I have always had a strong interest in disorders at the border of neurology and psychiatry, such as Alzheimer's disease, and Tourette syndrome, and Huntington's disease. In relation to Alzheimer's, Norm Foster and I were among the first to map

the cortical distribution of neuronal hypofunction using early PET scan technology. Most investigators at that time thought that the disease mainly affected the prefrontal cortex. But our results pointed more to involvement of the parietal and temporal association cortex. They seemed to fit the most typical clinical picture, as well as the distribution of cortical neurofibrillary tangles. Interestingly, when I first presented these data to an imaging conference in Stockholm, they were politely ignored. When I presented them several weeks later at a meeting in Bethesda, they generated rather heated criticism. Then a few months later, I listened in New York while a competitor presented what was essentially a concurrence with our findings, along with the claim of precedence. Fortunately, we had already submitted our findings to the *Lancet* and *Neurology*. And our pictures must have been attractive, since several drug companies later made use of them, without attribution or permission, in advertisements for their cholinesterase inhibitors. In the case of Huntington's and Tourette's disease, our work failed to make much progress towards finding better treatments. But my interest in these disorders did afford the opportunity to try new ways to stimulate clinical investigators to perform more scientific and less descriptive studies. In cooperation with the relevant patient advocacy organizations, my trick was to organize large international symposia to which leaders in research disciplines that could be important for a particular disorder, were invited. The first was on Huntington's disease, in 1972. Most of the invitees had never actually worked on the disorder being discussed. But, as hoped, many were tempted to apply their technology to have some results for presentation at the meeting. And publication of the proceedings of these symposia served as a stimulus to both investigators and granting agencies. I know these efforts were effective, since *Pub Med Citations* invariably spiked in their wake.

TB: So in the course of your research, you have become involved with cognitive function in neurodegenerative disease?

TC: Yes. I've already mentioned our imaging studies in Alzheimer's disease. My lab was also among the first to perform clinical studies with cholinergic system activators and inhibitors in Alzheimer patients, as well as in those with progressive supranuclear palsy. But I think your question was referring to my earlier comments about an interest in cognitive processing. In that regard, we have done some work, although not nearly as much as I would have liked. For example, Alan Braun and I conducted several cerebral imaging studies in Tourette's syndrome, which

attempted to link regional changes in neuronal function with the severity of various behavioral abnormalities. Perhaps the most interesting finding was an association between obsessions, compulsions, and coprolalia with hyperactivity in the orbitofrontal cortices. In the late 1990s, Chris Randolph and Eric Mohr and others in my group devised a neuropsychological screening battery known as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) that is now used in the assessment of cognitive disorders of various types. Now, getting back to neurodegenerative disease, our early work focused on the application of transmitter pharmacology to the development improved palliative treatments. But more recently our emphasis has shifted towards disease modifying, rather than just symptom modifying, treatments. Current molecular and cellular biology offer lots of powerful new tools and approaches to study neuroprotection and neurorestoration. I think the field is beginning to make some real progress, especially at the basic science level, even if the results from the large clinical trials of protective interventions have been uniformly discouraging. I've been putting together a list of pharmaceuticals that are available for clinical use and that have recently been found to act on mechanisms that could benefit some neurodegenerative disorder. These drugs, often older ones that are now off patent, would thus lend themselves to repurposing as novel disease modifying agents. Our focus has been on pharmaceuticals of potential interest for Parkinson's and Alzheimer's disease. The list includes more than 30 drugs.

TB: Was it as many?

TC: I came away with the feeling there are too many, not too few. There were more approaches to test than resources for testing. How could we rigorously prioritize all these possibilities? The drugs we first chose to work on had to act on a plausible disease mechanism and in a valid animal model, if one existed. They also had to act in the human brain in ways that could be measured noninvasively. It was essential to be able to establish acutely whether a safe and tolerable dose was able to exert an adequate effect on the putative target mechanism. Only then, would it be reasonable to invest the huge amounts of time and money that even a pilot neuroprotective trial takes. In the case of Alzheimer's disease, we are now looking at drugs that block a particular kinase, GSK (glycogen synthase kinase) 3, which mediates the phosphorylation of the microtubule associated protein tau at certain sites. The hypothesis is that the hyperphosphorylation of tau at these sites initiates a potentially injurious process of self-assembly into neurofibrillary tangles or

impairs axoplasmic flow. Although Alzheimer's disease is clearly multifactorial and heterogeneous, one or both of these mechanisms could contribute to the degenerative process.

TB: Are you working on this in your laboratory these days?

TC: Yes. We are currently looking at the ability of several common drugs, including lithium and valproic acid, to block particular GSK3 mediated phosphorylation reactions. Clinical trials in this area are beginning elsewhere, although I am dubious that any one of these GSK3 antagonists alone will confer clinical benefit to Alzheimer patients. It may be necessary to combine these drugs, or some additional drugs, in order to safely alter phosphorylation at critical tau epitopes in human brain. Working more with biologic markers, in this case tau in spinal fluid, might be a good way to start evaluating these therapeutic hypotheses, before launching a clinical trial. Mechanisms affected by these drugs could also be important for the treatment of other neurodegenerative disorders.

TB: Let me switch now to another topic. Could you say something about how you got involved with the ACNP?

TC: When I joined Irv Kopin's lab, I noticed that nearly everyone went off to some tropical paradise in December to talk science. The ticket for admission was merely a poster, which was easy to prepare, if you were doing full time neuropharmacology research. I found out that the meeting was organized by the ACNP and the next one was scheduled for Palm Springs. And so, I did what was necessary and went to the meeting and learned and enjoyed. And since then, I have done what was necessary so I never, or hardly ever, missed a subsequent meeting. Although the focus was always on psychopharmacology, I have never attended an ACNP meeting that was not full of exciting new brain science related to therapeutic issues of interest to me. In most ways, psychiatry has led in the development of better treatments for brain disease. Neurologists have much to learn from these successes.

TB: Is there anything else you would like to add? Is there anything we did not cover?

TC: Well, there are always more things to talk about. Now, perhaps they are best left for another time. But before ending, I should mention that I have been heard to complain that neurotherapeutics wasn't getting its fair share on the ACNP programs. The ACNP leadership usually responded by asking why I didn't propose sessions that would attract neurologists. So, I tried, once or twice, with little success in getting participants. Of course, there was a circular

problem. If there's no neurology, then there are no neurologists, and if there are no neurologists, then there's no neurology. The ACNP was doing just fine the way it was operating, and I was enjoying their meetings. If I wanted more emphasis on neurotherapeutics, then I would have to find another venue; which is eventually what happened. In 1997 I founded ASENT, The American Society of Experimental Neurotherapeutics, which joins the academic, government, industrial, and advocacy communities to facilitate progress in developing new therapies for those with neurologic disease. The organization is doing well, largely because it copied ACNP's successful formula.

TB: What would you like to see happen in the future?

TC: I think that trying to figure out what causes CNS neurons to die prematurely is very important. Neurodegenerative disorders can be regarded as a rate phenomenon. In Parkinson's disease, the difference between someone who evidences no Parkinsonism throughout a normal lifespan and one who manifests parkinsonian symptoms at age 60, is that the rate of degeneration of the latter individual's dopamine cells has increased by a factor several folds. The implication is that in Parkinson's disease, and presumably in other neurodegenerative disorders, just slowing down this accelerated rate could confer real benefit. Preventing onset or totally stopping progression is not immediately essential. I think the chances of discovering a way to achieve a modest degree of benefit are excellent in the near term. One or more of the newly emerging leads will soon begin to show efficacy. And even an initially modest success will transform the field of neurodegeneration, just like transmitter pharmacology did for psychiatry 40 years ago.

TB: I hope it will.

TC: I'm sure it will.

TB: And on this note we conclude this interview with Dr. Thomas Chase. Thank you very much.

TC: Thank you. My pleasure!

11. PAULA J. CLAYTON

TB: This will be an interview with Dr. Paula Clayton¹³ for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the American College of Neuropsychopharmacology, in Hawaii. It is December 9, 2001. Could you tell us where you were born, something about your education, early interests, and how you got into psychiatry?

PC: I was born in St. Louis, Missouri, in 1934, the third daughter of two parents who both went to college. The fact that they both had college educations was important. My mother decided, very early on, that I should be a doctor. She was an energetic woman who helped me pursue that goal. It never occurred to me that I wouldn't become a physician. When I graduated from high school, I went to the University of Michigan, graduated, and then entered medical school in 1956 at Washington University, which was in my home town, and where I was one of only two girls in my class. I felt they took me because they needed a second girl. It happened that I chose a medical school that was intensely interested in research, so we had to do research in our freshman year. Then, in our sophomore year, a very funny thing happened. We were just beginning our first course in psychiatry and the man in charge of teaching burst into the room and said, "We've just been approved for a rotation in psychiatry; now we've got to teach you about psychiatric diagnoses. We want you to come to class! You can't take it lightly! We're going to lock the doors, if you're not here on time." That man was Eli Robins. That was in 1957. So we went through a systematic approach to diagnosing patients for illnesses from depression and mania to schizophrenia, alcoholism, and so on. Eli would say things like, "The first thing you've got to decide when you see a patient is whether they have 'the big C.'" We all looked at him, dumbfounded, and he said, "Whether they're Crazy or not, because if they're Crazy, and that's the layman's word for it, they can only be depressed, manic, schizophrenic, organic or maybe have alcoholic hallucinations. That's the first thing you've got to decide." We were taught intensely about psychiatric diagnoses. That was certainly to my advantage, yet totally fortuitous. When we went into the clinic in our third year, in 1958, the faculty was beginning to use imipramine. So we were not taught about

¹³ Paula J. Clayton was born in St. Louis, Missouri in 1934. She received the M.D. degree, completed a psychiatric residency, and then became a member of the faculty of the Department of Psychiatry all at Washington University, Saint Louis. Thereafter, she became Chair of Psychiatry at the University of Minnesota where she served until she retired to a faculty appointment at the University of New Mexico. She was interviewed in Waikoloa, Hawaii on December 9, 2001.

psychotherapy. I only learned about making a diagnosis, basing a treatment on the diagnosis, and following the improvement of a patient's symptoms. A classmate of mine, who was first in the class, experienced a serious depressive episode. We were on the same rotation. You could just see him becoming less and less capable of answering questions directed to him. He was treated by a department member and after several failed drug trials, he was treated with ECT in his junior year. He graduated with our class. That shows how somatically oriented the department was. Before I graduated, I thought I wanted to go into internal medicine, but because psychiatry at Washington University was so similar to medicine, it became a possibility. I liked the people, Eli Robins, Sam Guze, George Winokur, and Lee Robins, in psychiatry, so I wondered if it would be a better area for me than medicine. I talked to my husband and to the faculty and decided, on the day I graduated, that I would do a residency in psychiatry. It was not something I went to medical school to do.

TB: It seems that your first encounter with psychiatry through Eli Robins had a major impact on your career.

PC: Right. And the lecture by Sam Guze on depression and suicide also had a major impact. The idea that we should ask patients whether they were suicidal when depressed, and plan a treatment based on that, was so foreign. Not just to me, but to all in the class. Everybody else said, one should not put ideas like that into the patients' heads, but at Washington U, they were insistent that every depressed and alcoholic patient had to be asked these questions.

TB: So, you were taught direct interviewing to derive a diagnosis. Everyone had to be asked specific questions?

PC: Yes, you had to ask questions. It was unique. The other unique characteristic was that we were taught that when dealing with inpatients, we should always interview their relatives before seeing the patients themselves. For really ill patients, relatives were considered more reliable sources of information about the patient's condition. There were only three of us who went into psychiatry, and we were probably the first generation of students exposed to that kind of thinking. When I began my residency, it was imperative to do research. No resident was allowed to graduate without a research project. I was encouraged and decided to do research on bereavement, because I knew what depressive patients admitted to the hospital looked like and I wondered how that state differed from that of those who were bereaved. First, I interviewed relatives of patients who died at Barnes Hospital. Then, I wrote a grant to do a bigger study, identifying people from death

certificates. Even though Washington U had a good reputation, they'd never obtained a grant to study a clinical issue before. So, they were very pleased that I did the project. Another important thing was that Eli, who was the chairman of the department, got intimately involved with everything we did. He was able to do that because by that time, he was ill with multiple sclerosis, which limited his ability to travel. So he taught me how to design a questionnaire for widows and widowers. He said, "Never ask open-ended questions. Think of all the possible answers, so that you give people an idea of what you want." That was interesting because the only open-ended question I did ask produced all kinds of answers that I couldn't put together in any quantitative way. He also taught me how to analyze data. At that time, there were no computers, so we did all of our "p" values by slide rulers. Because I was interested in depression, I also got involved in research with George Winokur, who at the time was doing a big follow-up study. From data collected in that study, we derived the diagnostic criteria for mania, which outlined the three main symptoms of the illness: a manic mood, push of speech, and overactivity. That was my first paper.

TB: When did you publish with George Winokur the diagnostic criteria of mania?

PC: In 1965. Then we did a follow up of those patients and wrote a book on *Manic Depressive Disease* that was published, in 1969. There were no computers, but George Winokur loved to work by hand in the card sorter.

TB: So you worked, at that point in time, mainly with George Winokur?

PC: Right. He was my major mentor. We also published the first American paper on the division of bipolar and unipolar depression.

TB: Didn't your book with George have a third author?

PC: That was Ted Reich. He was the junior author. I was the middle, and George was the senior author. Ted was a geneticist. He was born in Canada, studied there, trained at Washington U., and then went to England, I believe, to study genetics. He did the studies that showed bipolarity runs in families and that there are hypomanic gamblers and obsessional patients in those families. I was always most interested in treatment and wrote the clinical descriptions and treatment section in the book. At that time, lithium was already used; in fact, I used it first, in 1962. We had a manic minister, kind of like Elmer Gantry. He'd written bad checks. George read about lithium in *The Lancet*, and after the patient was given multiple ECTs and trifluoperazine, but was still not well, George had the pharmacy make up lithium pills, because nobody produced them. We gave lithium

to the manic minister and he got better. So, we began using lithium for mania, in 1962, even though it wasn't marketed and approved by the FDA.

TB: It took quite a long time after the first paper was published on the effectiveness of lithium in mania before it was approved for clinical use in the United States.

PC: Right. But the first paper was written by Cade, in 1949.

TB: Then, there were several papers published on it in the 1950s by Treutner and his group, in Australia, and Baastrup and Schou, in Denmark.

PC: Right. I was always interested in treatment; probably more because of George's mentoring than Eli, who was a therapeutic nihilist. For his entire career, Eli probably only used psychotherapy and Sodium Amytal (amobarbital).

TB: Could you say something about Eli Robins? He was a very important figure in American psychiatry.

PC: I did not know him when he wasn't ill, so I can't comment. But women, who knew him before then, said he was a very handsome, outgoing, and charming man. He could talk to you at a party about the movies you'd seen, or the last book you'd read. He was an intense thinker, who studied at Harvard in the early 1950s, and brought the scientific method to Washington U. His team of Sam Guze and George Winokur promoted a different approach to psychiatry than others did. They were not popular. I remember I was a resident and went to a meeting in Chicago, in 1962, with another colleague of mine, Dick Hudgens. They were promoting community mental health programs, saying that we needed to develop services in the community to prevent mental illness. Everybody agreed that pregnancies could be prevented with birth control and that infectious diseases could be prevented with vaccines, but my colleague stood up and said, "But we can't prevent mental illness. How in the world are you going to prevent mental illness?" It was that kind of approach that made everyone angry, because we asked piercing questions that people couldn't answer. Our Grand Rounds and Research Seminars were that way, too. You had to present research every year, and Eli would sit there and listen. He was sick and he couldn't hold his head up. Then, suddenly, he'd lift his head and ask a question that you were amazed at. You thought he was sleeping, and then he asked the most pertinent question. And you'd say, "Well, I'm sorry, I don't know the answer." Then, you'd go back and analyze your data to find the answer. It was a very provocative, enriched environment, in which to be a faculty member. And

it was very open. Except for those times when we had an outside speaker, we never had Grand Rounds without interviewing patients and discussing them. Eli would interview the patient or, when he got too sick, other people would. We'd discuss the treatment with everyone involved, and you learned that there's no perfect treatment. Depending on where you're coming from, you might treat the patient in very different ways. So, it was a helpful, nurturing environment.

TB: What about George Winokur? Could you say something about him?

PC: Yes. I told him once that I don't think he could have survived in the late 1990s, because he was so direct, to both men and to women. He could say the most awful things to you, and then laugh, and get away with it. When I was a resident, he said to me, "We'd like you to be chief resident." That was, in 1965. I hadn't thought of that, and I said, "Why should I do that?" And, he looked at me and he said, "Because it'll make a man of you." And then he laughed. He couldn't have said that, in 1995. He was in charge of the in-patient service, so he also interviewed every new patient the residents admitted to the hospital. He was also in charge of recruiting residents. I remember one of my junior colleagues telling me that he was interviewed by George, and at the end of the day, George called him into his office and said, "You know, you're not the best resident candidate we've ever seen or will ever see, but we'll take you." He was so direct that he would throw everybody off-guard. I saw him interact with a colleague, who was a dyed-in-the-wool analyst, and he'd say the most terrible things and get away with it. You certainly learned to be open and honest with George, and to admit when you didn't know something. I think the skills he taught me, did me well when I became chair in Minneapolis. It was Sam Guze, who represented the medical model in psychiatry for us. He was an internist before becoming a psychiatrist, and we learned from him the ways to validate a psychiatric diagnosis by information on clinical course and family history, treatment-response, outcome, and biological tests. He was also more serious. Once, I asked him if he wanted to have lunch with me. And he replied, "Only if you won't talk about your children." I was shocked, as I didn't think I talked much about my children. However, by the time he became Vice Chancellor at Washington U., he learned to be more tolerant of trivial talk.

TB: Could you say something about the relationship between Eli, George and Sam?

PC: They got along well. I think George and Sam lived in the same area of St. Louis, and for many years carpooled to work and, I assume, talked about psychiatry constantly. When Eli got

sick, George and Sam decided they would have to go to meetings and carry Eli's message. It was hard to tell, though, from whom the message truly originated.

TB: So, it was hard to tell from whom the message originated.

PC: I couldn't be sure. You know, by the time I was there, each had his defined area. We all read Kraepelin. So Kraepelin was our Bible.

TB: Do you know which edition of Kraepelin's textbook you had to read?

PC: I think the 1899.

TB: The one in which he introduced manic-depressive insanity and dementia praecox? PC: Yes. And the department paid for the book to be translated into English. And then we read things from Strömngren, Bleuler, and all those people. We were only taught evidence-based psychiatry. Every paper we read was based on data. We were not taught to be psychoanalytic, to think in terms of the unconscious or dreams, and things like that. So it was unique, and I always felt lucky.

TB: You were very lucky.

PC: I was lucky, also, that I was one of the few women. Eli Robins' wife, Lee Robins, was in the department, as well. She was a sociologist and did a very famous follow-up study that probably was Eli's idea. Lee became a real hero in her own right, but I don't know where she, or I, for that matter, would have been without being in that atmosphere. There was also another woman in the department, who eventually left. So, I was one of the few women, and it was an advantage. They put me on the lunch brigade with every speaker. And we had speakers from all over the world, a lot of Englishmen, people from this country, and Canada. I went to have lunch with them, being the token woman.

TB: Would you like to mention a few people whom you met?

PC: Well, Jules Angst is one. I later collaborated with him. Bob Kendall and David Goldberg from England are others.

TB: What about John Wing?

PC: Yes, I did meet him, as well. We collaborated and interacted with many people, including basic scientists, in several countries. Eli supported a basic science laboratory in the department, originally, with two basic scientists and residents and faculty who worked with them.

TB: What did they do in the laboratory?

PC: Blake Moore worked on protein chemistry and Bill Sherman worked on phosphoinositides and the mechanism of action in lithium. They had a mass spectroscopy. So we did original research on the relationship between dosages, blood level, and treatment response to first-generation antidepressants. I'm an author of a paper that reported that of all of the first generation antidepressants, nortriptyline was the one that you could depend on the most in terms of dose, blood levels, and outcome.

TB: Kragh-Sorensen in Denmark had similar data. Did you collaborate with him?

PC: No. His study and ours were parallel studies. I knew him, but we did not collaborate.

TB: I suppose by the time of these studies, the therapeutic nihilism in the department was gone?

PC: Well, Eli was really the only nihilist. John Biggs and another set of people did those studies.

TB: Are we talking about the late 1960s or early 1970s?

PC: I would think the mid-seventies. We would look at these drugs on the mass spectroscopy and see which were dirty and which were clean. I learned at that time, mainly through nortriptyline, to think about drug metabolism by the liver, because if you gave somebody 50mg of nortriptyline, the most common blood level you'd get was 50 ng. But if you gave somebody the same 50mg, and they ended up with 100 ng in their blood, you realized they must be a slow metabolizer.

TB: So, you and the department got involved in psychopharmacology, and especially, in pharmacokinetics?

PC: I never thought about it that way, but you're absolutely right. We started attracting residents who wanted to do these kinds of studies. Sheldon Preskorn and Matt Rudorfer came to Washington U. to train and took their own ideas forward. We also trained people like John Olney, Dave Dunner, John Feighner, Marc Schuckit, Steve Zalcman, and Ted Reich. Some of the people in the department got together and wrote up our diagnostic criteria, so they could be published.

TB: You are referring to the St. Louis criteria that Robins, Guze and Winokur formulated and John Feighner put in writing, in 1972.

PC: Absolutely correct. And, I think John would admit that. I was reading those criteria as a medical student, in 1957.

TB: Were you involved in the preparation of that paper?

PC: No. I would have liked to have been, but I wasn't. They met in Eli's office every Wednesday for months. Without John Feighner, that project wouldn't have been done, because Eli was ill, and

the other two were busy doing other things. It was John who said, “We really have to get this into writing.” So, they met every Wednesday and wrote the paper.

TB: The paper was written at those meetings?

PC: Exactly. Another interesting paper that Eli did was on the biochemical basis of psychiatric disorders. He wrote it with Boyd Hartman. Boyd went on to do wonderful research on norepinephrine in the brain, showing that it’s frequently on blood vessels. He got cows from the slaughterhouse to study their brains.

TB: Were you encouraged to do biochemical research?

PC: I only did pharmacokinetic research, but others, depending on their interests, did basic research. I left in 1980, but I can say that from 1956 to 1980, during the years when I knew what was going on in the department, we never did a drug company study. We were frequently invited to participate in these studies because we knew so much about clinical diagnoses, but we never accepted. On the other hand, the two collaborative studies of depression, one of which was a drug study, were the basis of my entry into this society.

TB: When was that?

PC: I would guess in the late 1970s; just before DSM-III was published. DSM-III was the product of many consultations. So Spitzer and Endicott came to Washington U. frequently and would stay for three or four days at a time, talking to Eli about it. I became a member, at the time, when neuropsychopharmacologists realized they needed an understanding of diagnoses. Many of us were admitted in those years as members in this College, so that we could be the critics of papers that dealt with clinical psychiatry.

TB: Were you involved in the development of the concept of external validity of psychiatric diagnoses?

PC: Eli gave a speech in the mid-1960s on external validity. I don’t know from whom the concept comes, whether it was Eli’s or Sam’s or George’s. But certainly by doing cross-sectional, follow-up studies, we all strived for external validity. Another thing that happened in the 1970s was that Eli got very involved as a consultant in both the clinical and biological collaborative studies of depression. There’s still a part of a project going on, on follow-up of those patients.

TB: Were you involved in those studies?

PC: Yes, because I was Eli's legs. He couldn't move; to go to a meeting was very difficult for him. So, he always had to have a collaborator go, and I was his collaborator on that project.

TB: But were you involved in those studies as an investigator?

PC: Yes, with the clinical study, but not the biological one. Eli had such an active mind. He also started a study on schizophrenia. It was about the time that Bob Heath, in New Orleans, put electrodes in the brain of schizophrenic patients to stimulate them. Then Arnie Friedhoff reported on a pink spot in the urine of schizophrenics and Eli decided to follow it up. He started it when he was well, and I followed those patients. It was amazing the criteria he used in the 1950s to gather this group. When we followed them up years later, if they had not committed suicide, they were still all schizophrenic. I remember going into the home of one woman and interviewing her. She seemed so normal. She was a mother and had children in school. I was using our structured questionnaire, and when I asked her if she ever felt that people interfered with her, she said, "Yeah, I really don't like to have people that close." And I said, "Why? What do you mean?" And she said, "Well, I don't like those people who come into my house, and comment on me, and tell me what to do." I had interviewed her for an hour and did not realize that she was psychotic. But once I got to psychotic symptoms in the questionnaire, she had every one. I didn't understand how she was able to function. It was amazing how she did so, with those strong auditory hallucinations and delusions in the back of her mind.

TB: They didn't seem to bother her?

PC: No, and her family seemed to accept it. I don't know whether she had any further treatment. The first part of the interview was general questions like, "Have you been in the hospital?" When I completed that part, I thought, well, this is the one patient that Eli really misdiagnosed; she is not psychotic. But there she was, psychotic.

TB: So the use of the structured interview helped.

PC: We were taught how to administer a structured interview and used one with every research patient. There were several competing structured interviews used in the department. However, the one that became the most well-known was the Diagnostic Interview Schedule (DIS).

TB: Were you also taught general psychopathology?

PC: We were taught psychopathology. I still have Fish's book and use it to teach residents.

TB: Didn't Fish come over to North America to give a series of lectures on psychopathology?

PC: Not that I know of. We were taught many things written by those descriptive psychiatrists. They were colorful and it was wonderful but we never knew who was right.

TB: Let's get back to your research. Your very first research grant was on bereavement, right? And you did this research sometime in the 1960s.

PC: Right, it was in the mid-1960s.

TB: Could you tell us more about that project?

PC: I found the people by using death certificates and identified the ones to be interviewed by using a random numbers table. We would call the people we wanted to be included in the study and then we would go to visit them within the first month after their loss. Then, we followed them up a year later. We found they had all the depressive symptoms that other depressed patients have, except as Freud already recognized, they did not have guilt feelings, they were not self-incriminatory and were not saying, "It was my fault," and that kind of thing. But they had sleep disturbances and weight loss. Some of them would lose 40lbs. They also had trouble concentrating and poor memory. They described their first response to the loss as numbness, which I think is the first response to any kind of stress or shock that could last from a few hours to a few days. Then they developed a severe depressive syndrome. They did not eat or sleep. The depressive syndrome dissipated in a year or so, although 10% of them remained depressed. These displayed a sort of a major depressive disorder without self-incrimination and suicidal thoughts.

TB: Then you analyzed, wrote up and published your findings. Was there anyone else at the time that did similar work?

PC: There was no one else, at the time. But we had a group of depressed in-patients who were being monitored. So I did compare my findings to what is seen in depressed patients in the hospital. They had similar symptoms except they also had guilt feelings and self-incrimination.

TB: You mentioned before that the first response to the loss was a kind of stress response? PC: I feel that bereavement provides a model for studying the response to stress. What we learned was that stress increased alcohol intake in some people. People, who took pills, took more; they took their own and their deceased spouse's pills, as well. And people who were inclined to overeat were eating more. Whatever characteristic behavior the person had under normal circumstances was increased, once they were under stress. In spite of their increased smoking and drinking, the

mortality rate of the widows and widowers was not different from the general population. To be able to study that, we had a control group of people who were in the same voter registry book, and of the same age. We had permission from the city to do that and identified them at the time the person died. They were in the same community with the survivors, sometimes even on the same block. We followed them for a year so that we could compare the mortality rate of widows and widowers with that of this group. The sample was small; it wasn't thousands, only 109. But there was no difference in mortality. So, we were interested in all aspects of bereavement. Since only 58% of those we identified allowed us to do an interview, we also had to prove that the people who refused were not systematically different from the ones we interviewed. After comparing them on all the things we could find in the death records, I thought maybe the people who refused were sicker and would die sooner. So I called them and said, "Hello Mrs. So-and-so, I'm calling from the *Post Dispatch*," which was our newspaper, and asked if they'd like a subscription to the paper. They'd either say, "No, I don't want it" or "I already get it," so at least I knew they were alive. There were four people whom I couldn't find because they did not live in the same house any longer. My data showed that if all of them had moved out of town and died, there still would have been no increased mortality among those who refused an interview.

TB: How was your report received?

PC: It got mixed reviews. Danny Freedman accepted the first report for the Archives without sending it out to reviewers. There was some controversy because one of our papers showed that Lindeman's idea of acute death and the syndrome that followed was not valid. Another study on anticipated versus unanticipated grief showed no differences, which was upsetting to some.

TB: Did your finding stand up over time?

PC: Yes, absolutely. And it's important that it is a model for stress.

TB: Stress caused by death?

PC: Yes. I recently wrote a paper titled, "Why People Should Use Death as a Model for Stress." I have never understood why animal researchers didn't take a pair of animals, remove permanently or kill their mate, if that is acceptable, and study the animal's physiologic responses. There's one nice study on noradrenaline responses in men whose wives were dying of cancer. Some of the wives died and some didn't, so it was possible to study bereavement response.

TB: Did you look at sex differences in the bereavement study?

PC: We did. We looked at everything. We looked at length of marriage, sex differences, and religious affiliation. There were very few sex differences. Women had a little bit more insomnia but the overall responses were amazingly similar. Men cried less frequently than women, but for the most part they had the same responses.

TB: So you eventually moved from studying stress and bereavement to studying manic-depressive illness and genetics?

PC: Actually, I was doing those projects simultaneously. I did the study on stress and bereavement on my own; the one on manic-depressive illness was in collaboration with George. I was also involved in the cross-sectional and follow-up study of 500 randomly selected outpatients. I have to say that Washington U had a very different model of education than most universities did at the time, in that they thought that young people needed to do research and the older people should do the teaching, because younger faculty needed to make their mark in research at a young age. So we were allowed a lot of time to do research and had very few clinical responsibilities, which is totally different from what universities do now. Now, what the residents do is mainly clinical. What we did at Washington U. was good. And there is something I have not mentioned yet – I had three children and didn't work full time to begin with. It was really fortunate that I didn't have any strong ongoing clinical responsibilities, because I wasn't there half the time! They couldn't assign me to a ward to take care of patients, because I only worked Tuesdays, Thursdays and Fridays.

TB: Weren't you chief resident at Washington U at the time?

PC: Yes. Actually, my ex-husband should be given some of the credit for that decision. When they asked me to be chief resident, I went home and said, "Gee, they've asked me to be chief resident. Do you think I should do it?" And he said, "Well, they're awfully nice people." He thought it was a good idea. I hadn't thought of staying in academia before that happened, because the natural course was that if you were chief resident, you would go on to become a member of the faculty.

TB: What did you intend to do?

PC: I hadn't really thought beyond residency. I don't think I ever thought about practice and I certainly didn't think about being chief resident. I might have thought about staying to help somebody do research. You could do that. But then I got involved in the follow-up study on mania.

TB: Did this happen when you worked halftime? When did you actually work halftime?

PC: Maybe from 1965 to 1972, or something like that.

TB: Didn't you write your first book, *Manic Depressive Illness*, during that time?

PC: Yes, it was published by Mosby, in 1969. There are many research findings in that book that have been reconfirmed over the years. TB: Could you tell us something about the book?

PC: It was based on a follow-up study of 61 patients, all with manic depressive illness, who we had identified. George had done the work originally. I did the follow-up. My former husband was also helpful at the time. He was an attorney and asked me, "Why would anybody drive from Springfield, Missouri to interview with you? How can you ask these people to come back?" I said, "I really don't know, but they do!" Then he said, "They want to tell you their story." I realized he must have been right. It was an interesting adventure and I learned that follow-up studies are essential. That was the other thing that Washington U championed.

TB: Didn't that follow-up study draw attention to the fact that psychotic symptoms in mania are indistinguishable from psychotic symptoms in other psychiatric disorders?

PC: My first paper based on that study dealt with psychotic symptoms in mania and it showed that manic patients have as many psychotic symptoms as schizophrenic patients do. When it came to diagnosis, there was nothing pathognomic about psychotic symptoms. In the book, the study clearly showed that psychotic symptoms are not unique to schizophrenia and that they also occur in mania and depression. We also did a follow-up study and a family study. We interviewed every member of the patients' families and wrote the book on the clinical picture, clinical course, family history and treatment of manic-depressive disorder; but first, we did a thorough review of the literature up to that time. The book is especially informative because the course of illness was less influenced by pharmacological treatments at the time. We found that one-third of the patients had their first episodes before age 20, none after the age of 50. Most of the family members were depressed.

TB: Is there anything else you would like to tell us about Washington U. before we move on to the next chapter in your professional life?

PC: Two things, actually. One, we were a very social group – the department members threw lots of parties at their homes for faculty and residents. Two, we were always encouraged to go to meetings. Not only were we encouraged to attend, but Eli actually paid for us to go to them. I

remember the first meeting I went to in England, where I presented on bereavement. I presented annually at the APA and at many other prestigious meetings. I met a lot of people. Then, when Sam Guze became Chairman of the department, he said to me, "You know, I really think you should be a chair person." When I asked why, he said, simply, "Because I think you'd make a good chairperson!" By that time, I was sort of "second in command" in the department; he was both Chairman of our department and Vice President of the University. I was the one in the department to whom people would complain. It was also Sam, who told me, "You've got to go and interview for jobs, even if you don't want them. You've got to interview. You can go once and find out about the job. Don't go back if you're not interested but go once and learn the process." So I did that. I went to Buffalo, to Irvine and maybe a third place, but I felt the problems in those departments were insurmountable and I didn't go back to any of them. Then I was invited to go to Minnesota. It had always had a tradition of research and they had a good department of psychiatry. Don Hastings had been an earlier Chairman and he'd taken care of a lot of important people. He had a special research budget for the department. Len Heston did his early research on schizophrenia and Alzheimer's there, and since the department was in a place that used to be a psychopathic hospital, they also had a budget from the state. So the department had a very hefty budget.

TB: Was Hastings the successor of Bert Schiele?

PC: No, actually Bert was never a chair. Bert had retired by the time I went, but when he was there, he had a research unit. There were studies going on, on anorexia under Elka Eckert and Heston. They had a really good research program that I could identify with. I went back for the second time and finally decided to accept and become the chairperson.

TB: When was that?

PC: That was in 1980 and I did that for 19 years. Actually, Gerry Klerman told me that he had interviewed for the chairmanship; eventually they hired a person from the army who succeeded Hastings. This interim chairman, whose name I won't mention, was a good clinician, but not a researcher. He had no interest in research. At the time he took over the chairmanship, he asked Bert Schiele, "Well, why do you get grants to do studies when the state will pay your salary?" He couldn't understand. He had no concept of research. When he left, we re-started research. But, in the meantime, the psychologists had been very active in the department. Hathaway, who devised

the Minnesota Multiphasic Personality Inventory, was there. Paul Meehl was also in our department. We had a whole host of strong researchers. So we reinstated psychiatric research in the department, I think, successfully.

TB: Did you continue your research in pharmacokinetics or any other area of psychopharmacology?

PC: I really have to say, I did not pursue that. I've always been more of a clinical epidemiologist, and so the grant I wrote in Minnesota was to study elderly depressed people, because I wanted to learn what kinds of activities they were engaged in. I didn't get that grant. They thought it was too ambitious. After that, I mainly pursued psychopharmacology through the ACNP and work with pharmaceutical companies. I did not do drug studies myself, but our younger faculty members started to do clinical trials. I remained interested in the genetics of psychiatric illnesses, but I didn't pursue that line of research either. I was also still involved in the data analysis of all the studies I had worked on at Washington U., so I continued to write manuscripts.

TB: Didn't you do some studies with the dexamethasone test in anxious depression?

PC: Yes. Max Hamilton was another good friend and it was evident from his questionnaire that anxiety is a very significant part of depression. So, I used collaborative study data to write about anxious depression, and then, collaborating with Bill Miller, used Iowa data in a study in which we compared dexamethasone suppression in anxious and non-anxious depressed patients. We used a scale derived from the SADS items. We found that anxiously depressed patients were the most consistent suppressors of the morning rise of cortisol. That shouldn't have been too surprising. The HPA axis reflects anxiety and not just depression. I pursued clinical ways to validate diagnoses, but not any neuropsychopharmacology.

TB: Could you tell us something more about the collaborative study you just referred to?

PC: It was a NIMH collaborative study, an enormous undertaking. It was pivotal in developing assessment instruments that are still used today. It was difficult because there were five centers – Chicago, Boston, New York City, Iowa, and St. Louis – as well as NIMH. We were five sets of strong investigators and we did well. Gerry Klerman was a wonderful leader because he was so tolerant. He would listen to everything and then make a decision. He had a tendency to get a little impatient, so the discussions couldn't go on forever. It was a very important study in confirming the age of onset and course of bipolar and depressive disorders. It also established lack of

difference between different subtypes of depressive disorders. Marty Keller was part of that study and, of course, Bob Hirschfeld. Bill Coryell and Nancy Andreasen were also involved, as were Bob Spitzer, Jean Endicott, and Jan Fawcett. It was a study that taught people about research. Marty Keller was a resident when I first met him and now he's the Chairman of the Department at Brown. All of this is important for appreciating the scientific value of that project.

TB: Didn't you do some research with Jules Angst in Zurich?

PC: Yes, and that was wonderful. This month, we will be publishing a follow-up of his original bipolar and unipolar cohorts. He has been collecting data on these patients from their first intake interview to their death. And he has already shown that in each depressive episode, there is an equal chance that the patient will commit suicide. An interesting part of that study was related to clozapine. In spite of the reported cases of agranulocytosis in Finland, clozapine was not taken off the market in Switzerland because they found it so useful in hospitalized patients in Zurich. Angst's studies show that if bipolar and unipolar depressed patients are maintained on medication, that includes lithium, antidepressants, and antipsychotics, their suicide rate is enormously reduced.

TB: You worked with him on this study.

PC: I collaborated with him on this and on another study. In the other study, he administered a German personality inventory, in which many dimensions were measured, to all men inducted into military service in the canton of Zurich, Switzerland at the age of 18 and followed their psychiatric history throughout their service. We went through all of those records and used Feighner's criteria to re-diagnose those patients who got psychiatrically ill. We also looked at their personality traits. It turned out that unipolar depressed patients, prior to the onset of illness, had personality traits characterized by more aggressiveness than controls, whereas the personalities of bipolar depressed patients were not different from those of controls.

TB: Did you work with him on any other projects?

PC: No, these were the only two in which I collaborated with him.

TB: What are you doing these days?

PC: I retired in July of 1999, moved to Santa Fe, New Mexico, and began teaching in the outpatient clinic as a volunteer. Last year, I decided I was not doing well with retirement and needed to get back to work. I missed being mentally stimulated and thinking about research issues. In September of this year (2002), I started to work halftime at the University of New

Mexico and I'm a Professor in the Department of Psychiatry. I drive from Santa Fe to Albuquerque and teach in the outpatient clinic, see a few patients, and then try to mentor residents, mainly women. We just wrote a grant to study the treatment of depressed bereaved patients with Lexapro or with a placebo. There is another group in the US involved in the same kind of research; if we get our grant, I think we will write a proposal for a collaborative study and try to get funding from a pharmaceutical company. Since September 11th, it has become very important in cases of death and trauma to determine when psychiatric medications are necessary and what treatment is most appropriate for each patient. It's a very timely grant, at this point.

TB: It seems that you are trying to get back to research?

PC: I started with research and I'm going to end with research. All I did in between was administration, and I didn't find that pleasing. TB: Seventeen years of administration?

PC: Nineteen. When I first went to Minnesota, I asked the head of surgery, "What do you expect of a psychiatrist?" And he said, "I want them to see my consults on time." That was not at all what I expected him to say. By the time I left, people appreciated the significance of psychiatry in medical school. The Dean told me, if he had to do it over again, he would have become a psychiatrist. I think they did finally feel that psychiatry was a part of medicine and could bring in research dollars. Our budget in Minnesota went from three hundred thousand, when I started, to eleven million by the time I left.

TB: It sounds like you were a very successful Chairperson.

PC: I just had good people. You hire some good people and you hire some bad. That's what Tom Detre taught me. He said, "Paula, for every eight people you interview, you'll get one good one." So you hire them and you really try to support them.

TB: What do you consider your most important contribution?

PC: I would say establishing the definition of mania and the book on bipolar disorder, published in 1969 – which was really George's idea – but we executed it together. The whole idea of studying normal people in bereavement to find the psychological response to such an event and the subsequent outcome was also very important to me. Those would be my two. I wrote the first paper on schizoaffective disorder in this country. Some people still ask me to come and speak on schizoaffective disorder, but it's not a subject I've pursued. I also published on depression in women physicians. Another interest of mine is anxious depression. Those are my favorite subjects.

TB: What was your last publication?

PC: My last paper was with Jules Angst on his bipolar study; I'm a middle author on that article. My last sets of papers were on anxious depression; on the family history, treatment response, and things like that from the collaborative study, and then on the biologic markers in that study from the Iowa data. One other thing has dawned on me in recent years, about entering academia - I really feel it's extremely important. It's sad that people don't enter academia, particularly, women. I was married to a man who had to go to work every day to make a living. He was not salaried and he taught me how fortunate we in academia are to get a monthly salary and benefits. He said, "Well, Paula, I can't go with you on your trips. If I don't work, I don't make money." In academia we can do all this traveling and have all this freedom because we have people to back us up. We are salaried and encouraged to do those things. It's a very wonderful life. It gives you a lot of freedom. It's worthwhile to take these lower academic salaries and have this enormous freedom compared to having a higher salary and getting stuck in one place forever and ever. So when residents come to me and say they like academia and research, and especially, if they have published a paper, I say to them, "Try academia if you can afford to do it. It really is a wonderful job, and you meet all these wonderful people, and you're on the cutting edge." I have never felt that I made a mistake in my decision to become an academic, and it wasn't because I thought it through. It was just being in the right place at the right time. I believe that more people, especially women, should go into academia.

TB: So it was people like Eli Robins and Sam Guze who stimulated you to become an academic?

PC: And George. I think it was George. George was the one who asked me to be the chief resident, in his crazy way, and that was my entrance. My early research with him played an important role. He was my mentor. He had a way of teaching. We had rounds with him three times a week to present new patients each time, at the end of those rounds, he assigned one of us a subject that we had to read and report on. I said to him one day, after presenting a depressed patient, "How does this patient differ from what you feel if you lose someone?" And he said, "I don't know. Go read about it." And, of course, I went and read Lindeman's work, because he was one of only three major contributors to the area, along with Freud and Abraham. When I presented what I had read to him and the group, he said, "Well, that would be a good project."

That was to become my research project as a resident.

TB: As Chairman, were you involved mainly in administration?

PC: I couldn't do much research. I didn't have time.

TB: How did you support the research units in your department?

PC: Through grants and donations.

TB: How much teaching did you do?

PC: That's a good question. When I became chair in Minnesota, there was only an elect clerkship in psychiatry. So, the first thing I did was work on getting a six-week clerkship. That was important. I had a very good faculty teacher whose father had been a teacher of chemistry. He was a very bright guy, who didn't do a lot of research but was extremely scientific in his approach to questions. And he took charge of teaching. I always lectured in the freshman course and lectured in the second year, on depression or mania. So I did do some teaching. I also interviewed all the prospective residents. And of course, I always taught residents in various rotations.

TB: Did you use the model of Washington U?

PC: Yes. I established Grand Rounds, where we discussed clinical cases and at times, brought in scientific speakers.

TB: Did you encourage residents to combine research with their clinical work?

PC: I couldn't quite adopt that model but I tried. When I was half-way through as chair, we established a clinical track, and I called all my faculty on the tenured track together and said, "I think we should hire people to do the clinical work, so that you have more time to do your own research, but the only way I can attract people to do that is to pay them more. Now, what would you think if I hire an assistant professor in the clinical track who makes \$20,000 more than you?" They assured me that that would be acceptable to them. So we did it, and that freed up the time for people on the tenured track to do more research.

TB: How much clinical work did you do while you were Chairperson?

PC: As Chairperson, I was involved in clinical work with the residents. Each of us spent two months a year on the inpatient service. I even spent one month on the eating disorders unit, a clinical area I had little knowledge of. After we started an outpatient clinic, I worked half a day in the clinic every week. I also started a mood disorder clinic, where I supervised residents. I also saw a number of patients for medication combined with psychotherapy; probably five or six every week.

TB: So, you were involved quite a bit in clinical work?

PC: Right. I've never stopped and I've always seen patients. Another thing I did in Minnesota was what Sam taught me, which was that there would always be grateful patients, and so, it's very important to think about asking people, in the right way - maybe through the alumni offices - to give money. We did raise money for two endowed chairs and two professorships and some other things.

TB: You mentioned that currently you are mentoring, and I felt that you were emphasizing that you were mentoring women psychiatric residents?

PC: I was hired because women comprise half of most faculties now, and those who are good, don't have time to supervise. There's a wonderful woman professor at the University of New Mexico, but she's busy. She cares and is a great teacher, but she's busy doing everything else. So she felt that I could have the freedom to do this. I think women need more encouragement, mainly because they're caretakers. Women are – by nature and by nurture – caretakers. It is easier for them to take care of patients than to do research. They may not be quite as competitive or as thoughtful about the world out there, so they need more encouragement to do research. That's why I stress the point.

TB: Is there anything else that we didn't cover? I have one other question that is related to your involvement with ACNP. You have served on several committees of the College; could you tell us something about that?

PC: ACNP is run by people actively involved with the organization, so I was one of them. I had been a member and chairman of the membership, ethics and education committees. I was on the council for several years. And I was involved in a long-term project that evaluated what training psychologists – PhDs – might need to be able to prescribe medication. That was quite a commitment. We went to Washington and all over the country. As I said, I've been very active.

TB: Aren't you also involved with other organizations, like the American Psychopathological Association?

PC: Yes; I am actually a past president of that organization, as well as the Psychiatric Research Society and Biological Psychiatry. The only other one I have been active in is the APA.

I'm on a whole host of APA committees.

TB: Weren't you involved in the editing of the APA journal?

PC: I was, but not anymore. But I have been on the committee that works on practice guidelines for some time now.

TB: Is there anything else you would like to add?

PC: Although I have mentioned my ex-husband and my children, we haven't talked about the fact that I was in medical school, when I got married and had my first child. My mother was over 40 when I was born, and as a consequence, was not as involved in my life as I would have liked. I got it in my head that I wanted to be a young mother. I had my second child during residency, and my third at the end of my residency. At the time, I felt like the people around me accepted it. Now, when I talk to my former teachers and I ask them how they felt about it, they say, "Oh, we had long discussions about whether you could be pregnant and be a resident!" I was shocked. It was something they thought might be difficult, but it was possible. Now, I have five grandchildren and two of my three children are married. One is a doctor and two are attorneys. My life is proof that you can do all of these things. But you have to prioritize what is important to you, and I learned that very early on. I once was asked to do a computer program for a lot of money, early in the 1970s, and I said that I would do it. I sat down one weekend and tried to write a program, but I didn't like it - I thought, "I'd rather be with my kid." So I called them up the next day and said, "I'm sorry, I can't do this." Around the same time, I was asked to be President of the Missouri Psychiatric Society, which would have meant driving to Jefferson City from St. Louis, so I said no. I think you have to prioritize, especially if you want to be both a mother and an academic.

TB: On this note, we conclude this interview with Dr. Paula Clayton. Thank you very much for sharing this information with us.

12. ROBERT A. COHEN

TB: It is November 2, 2000. I am Thomas Ban. We are in the home of Robert Cohen,¹⁴ in Baltimore, to interview him for the archives of the American College of Neuropsychopharmacology. Could you tell us where and when were you born, something about your childhood, early interests, and education?

RC: I was born in Chicago, and as I mentioned to you before we started this interview, I was run over by a light truck at the age of 10 and had a fracture of my femur very close to its head. The truck ran over my abdomen and I was in the hospital for ten weeks, something that would be impossible now. At first, the doctors were quite concerned as to whether I would make it or not, but actually the only serious thing that happened was the fracture. After two weeks in the hospital, it was clear that I was going to recover. But the recovery was rather slow and this hospital was the hospital in which I was born. The nurses and interns had spoiled me in the hospital. They spent a lot of time with me, joking with me, talking to me about various things. And by the time I left the hospital, I decided that I wanted to be like them; so I began to think about how I could possibly become a doctor.

TB: How old were you when this happened, ten?

RC: Ten.

TB: So, it happened in 1919, right?

RC: My family was a typical family of that time. My grandparents had come to the United States from Prussia, around the 1880s. We were two boys and five girls, and like many other Jewish families, the girls went to high school and the boys went to college. I knew that I was going to go to college from the time that I can remember. My mother had hoped that I would be a lawyer, but I rebelled, and became a doctor. After graduating from high school, I went for a year and a half to Crane Junior College, which was the Municipal College of Chicago. When I was admitted as a junior at the University of Chicago, I registered for a new course in physiology, which was given by Ralph Gerard. Gerard had just come back from a National Research Council scholarship

¹⁴ Robert A. Cohen was born in Chicago, Illinois, in 1909, and received a Ph.D. in physiology and an M.D., simultaneously from the University of Chicago, in 1935. He served at Chestnut Lodge Sanatorium in Rockville, Maryland, from 1947 to 1953, then until 1981, was a senior administrator at NIMH. Cohen died in 2009. He was interviewed in Baltimore, Maryland on November 2, 2000.

in Europe, where he had worked for six months with Dennis Hill measuring the speed of the nervous impulse.

This was a fascinating course with no formal lectures. The first day, when Gerard had come into the laboratory to a relatively small group of about twenty students, wearing a rather dilapidated lab coat with many acid holes in it, and smoking a big fat cigar, he asked us: "What is life?" And we began to try to give our answers to this unexpected question. And whatever we answered, he asked: "how would you prove it?" Then he asked the students to criticize each other; that, to make a long story short, stirred up my interest. Looking back at it, he really opened a new world for me. In the laboratory, we saw an assortment of animals. While he was moving around, he got us talking, and ultimately, we had to choose our research project. There were two requirements. One, we had to get his permission to start it, and two we had to get his permission to stop it. My project was to measure the blood pressure of a frog. We made a little hemostat to register the blood pressure, then gave some adrenaline and found sometimes that the adrenaline made the blood pressure go down instead of up. We never found the answer why. We also found the paper by Roy Hoskins, which indicated that it could have something to do with the biochemical state of the nervous system, at the time the adrenaline was given.

Gerard then became my counselor in my courses. In some way, I feel grateful to him, because certainly what happened to me, would not have happened with anyone else. But he also deprived me of an education because he advised me which courses to take. He decided that maybe one course of philosophy would be useful, so I had a course in philosophy. I had also a course in English history, because my father had been born in London, and I wanted to know something about English history. And I took one course in anthropology from Edwards Supeer, who was a distinguished anthropologist. All the rest were courses in science and languages, i.e., German and French, in order to get a PhD.

I finished the first year of medical school education before I graduated from college. During my first year of being in medical school, I had already taken many of the courses that my other colleagues were taking, so I began to do research then; Wade Marshall and I shared a laboratory. The people at Washington University had just demonstrated the shape of the nervous impulse and Wade was building a machine to reproduce that. And I was trying to see whether it was possible to restore conduction in nerves, if one used a hydrogen acceptor rather than oxygen.

TB: Am I correct that we are in the early 1930s at the University of Chicago and that the findings of your research were to become your first paper?

RC: Yes. We demonstrated that it was possible to restore conduction with metadine (3-phenyl piperidine) and we published it in a paper.

TB: Do you remember the journal it was published in?

RC: Probably the *American Journal of Pharmacology*.

TB: And what did you do after that project?

RC: I became interested in studies of nerve metabolism and moved over from the laboratory that was on the east side of Gerard's office, to the metabolic laboratory on the west side of his office. There was a girl there that I was very attracted to, I must say, and she was also doing metabolic studies, and between us, we shared an apparatus. Mabel had it Monday, Wednesday, and Friday and I had it Tuesday, Thursday, and Saturday. And ultimately, in 1933, we got married. She was a year behind me in school, but we both finished at the same time in 1935. Let me go back for a moment. Before graduating, I was seriously wondering whether I should get my medical degree. Nineteen-thirty-four was the depth of the Depression. But Dr. Carlson[Anton J.], who was the Chairman of the Department of Physiology, strongly advised me to get my PhD in physiology and go on to complete my studies for an MD, as well. Jobs were very hard to get in those years. Dr. Carlson was the President of the American Association of University Professors, and he thought that one would be better off having an MD and a PhD. One of the advantages of working for a PhD was that if you became an assistant that paid a thousand dollars a year, and the tuition in those days at a medical school was three hundred and seventy five dollars a year. So, when Mabel and I got married, we had an income of two thousand dollars a year and only seven hundred and fifty went to medical school. We could live very comfortably on twelve hundred and fifty dollars, which we did. We got through medical school, owing the University only six hundred dollars at the end. Everything else was paid for.

One of the courses I assisted in was Dr. Nathaniel Kleitman's. About three years ago, Dr. Kleitman died; as you can imagine, he was 105. He was working on sleep. He and Aserinsky were the ones who described rapid eye movement (REM) sleep, first. One day, Dr. Kleitman told me to give the lecture on the physiology of behavior. I was able to read about everything that he recommended and in two hours I gave a digest of that. I thought, at that time, well, wouldn't it be

interesting if somehow or other we could do studies of brain metabolism in human beings, but I had no idea how this was going to come about. This caused me to look into psychiatry as a possible field, where one might get involved in research. But the University of Chicago didn't have any psychiatry, at that time. Roy Grinker was Assistant Professor of Neurology, and the University had sent him to study psychiatry in Austria. He was analyzed in Vienna by Freud. He was to come back to the University and start the Department of Psychiatry. This is what he actually did, but he soon left the University and went to Michael Reese Hospital. He arrived at Michael Reese Hospital to take over the neurology service, where I was an intern at the time. After his arrival, all the members of the Neurology Department had resigned, and Grinker took over the service and established his new Department of Psychiatry. By the time I returned to Chicago from my internship, Margaret Wilson Gerard, the wife of Gerard, had been analyzed and became the first child analyst in Chicago. We had spoken to her and she recommended that I come east to get training in psychiatry. So, I applied at Johns Hopkins where Adolf Meyer was the Professor, and was accepted there. Mabel came as an intern at Baltimore City Hospital. We were thinking then of going back to Chicago after we finished our training. During that first year, we were going to the Medical Society meetings, and were fascinated by Dr. Joseph Gesell's talk, and I thought that I ought to at least find out something about psychoanalysis. So, I decided that I'd leave Phipps Clinic and go to Sheppard Pratt Hospital, where Dr. Gesell was a psychoanalyst. He was also a graduate of the Union Field Seminary and had a PhD in psychology. So I suggested to Mabel, who was thinking of internal medicine, that she ought to have at least a year also at Sheppard Pratt. We started out at Sheppard with some misgivings. Dr. Meyer was a little bit angry with me, at first, because I went to Sheppard Pratt. But then, when he would come as a consultant, they always had me take him around. Later, he wrote me a letter saying that "we were sorry to lose you, but I see that you are not lost." We stayed at Sheppard Pratt a year and were planning to go to Chicago to continue analytic training. Back in Chicago, I went to the Institute for Juvenile Research and Mabel went to Michael Reese Hospital. But we were troubled by the situation in Chicago, because there seemed to be a great deal of hostility between the two groups in psychiatry. The group in Washington seemed to be more congenial, so after a year, we came back to Sheppard Pratt Hospital.

I had joined the Naval Reserve. The recruiter from the Naval Reserve came around while I was at Hopkins and told us about the glories of serving in the Navy, and said that if a war should start, they'll call the whole group, so we would serve together and that seemed like the reasonable thing to do. But in July 1941, I got a letter from the Chief of Naval Operations, asking me to report for duty at Norfolk Naval Hospital, in September of 1941. This was three months before the war started. It turned out that the Chief of the Psychiatric Service at Norfolk, Dr. Kennedy, became the Senior Psychiatrist in the Navy. So, this was in a sense a great opportunity for me. Lawrence [Coleman] Kolb, whom I had known from Phipps Clinic, was in neurology when I had been there, reported for duty a couple of months after I did. And Donald Dodge, who had been chief resident at New York Neurological, reported for duty also. The three of us really had a marvelous year together. Our training was not very much, but each of us had had experiences that the others did not. And we got along extraordinarily well. We turned out a tremendous amount of work. It was on that basis that Dr. Kennedy, Chief of Psychiatry, assigned us to jobs that he thought we were particularly interested in and would make the most for ourselves, and the Navy.

And then, the last year and a half of the war, I was assigned to the OSS, which was a special unit that was examining people who were going overseas. There, I became acquainted with a very large group of psychologists, many of whom were very gifted academically, so I got acquainted with psychology at that time. Mabel didn't follow me around. She had gone to Chestnut Lodge to practice while I was gone, and when I came out from the Navy, I decided to go to Chestnut Lodge, too. I was there for a year. Part of that time, I did half time practice, and then, became interested in the treatment that they were attempting to do with very sick schizophrenic patients.

I met Dr. Felix, at that time, because I was a member of Frank Braceland's examining team on the American Board. Felix was very interested in psychoanalysis. He thought that as Director of AMA he ought to know what psychoanalysis was about, and so, he went into psychoanalysis with Frieda Fromm-Reichmann. And since I had also been analyzed by Reichmann – I can't see any other reason why – he asked me, in the summer of 1952, whether I would be interested in coming to the National Institute of Mental Health to set up the psychiatric research department. TB: You were a psychiatrist with a background in physiology. By that time you had also published several papers.

RC: Yes. At the time, I had some doubts whether psychoanalysis was something I wanted to spend the rest of my life doing. So, I asked him what he had in mind, what sort of research. “Well, we will have a building and there are going to be a hundred beds that you can have and you can do anything you want. The salary will be fifteen thousand dollars a year for you, and we might be able to get one or two other salaries and people” – but he wasn’t sure about that. “You can go anywhere in the world that you’d be interested in going; the government will send you; you can invite anybody you want to have come as a consultant and the government will pay for it. The job is full time; no teaching, certainly no practice. The building should be ready by March of 1951. We promised that we would open.”

And so, I agonized about it. It was not about the job itself, which seemed to be a fantastic opportunity, but I wondered about many things, including that I was making somewhere close to thirty thousand dollars. That didn’t bother me because Mabel was in practice, and we didn’t need to have two incomes, and she said if you want to go, don’t hesitate for that reason. But I wondered how we would get anybody else to come, who wasn’t in that position, where money was no object. So I talked and agonized. The Lodge was going very well, then. We’d brought together quite a good staff of people. So, first, I thought “It won’t work” and I said, no, I would not come. But Felix did something which I later learned was very clever as a way of recruiting; if somebody takes a long time to make up his mind, and says no, he’ll have some doubt about it, if you ask him again. So he asked me again. I felt a little bit as if Columbus had asked me to help him discover America. Would I have said, “Well, things are going so well here in Genoa that I can’t come?”

So, I went and took the chance and the one thing that I did learn is that nobody I ever hired came for less than he was already earning. I actually reported for duty on December 30, 1952. I talked to a number of senior people, who were being called up at the time to serve in the Korean War, and to a lot of residents, at very good places, who were being called to active duty, because I thought, between the two, we’ll get good people; and if they stay for two years, some of them will do good work and can stay, and maybe some of the others will get so involved that they’ll stay, too. Then, Eisenhower ended the Korean War and all the senior people called up and asked, “Well, I don’t really have to come, do I?” And I said, “of course not.” So, I started with great anxiety, but determined to give it a try.

I remember the very first day, I reported, as I said before, on December 30th, the very end of the year. Edward Everett and Josephine Sams, his wife, and I were sitting in an empty office; most of the people were away for the holidays and they came in and talked to me about what we were going to do and about what they would like to do. I always had a special relationship through the years with Ed Everett, who died tragically, and his wife. Ed was just a second year resident in psychiatry, at that time. The first years were very, very difficult, trying to bring together a more mature staff, and I had to wonder what are we going to try to do?

TB: I understood that you were invited by Robert Felix to set up the research department in psychiatry. Were you in charge of clinical investigations?

RC: Yes. Seymour Kety originally had the idea that he would bring together both the clinical and basic research staff, but he found that he was having difficulty in recruiting people. When I was introduced to Seymour, he was serving as the Scientific Director for Neurology and Psychiatry. Wade Marshall, who I knew way back from the Gerard days, was there as the Lab Chief in Physiology; and John Clausen was there, whom I'd known at the Institute for Juvenile Research, as chief of Social and Environmental Studies. And then, I became acquainted with David Shakow and told him that we needed to get some psychologists. He became very interested in helping me. I had known a whole group of psychologists from my OSS days, and I would approach one after the other, but they'd all say, no. And Shakow, who was trying to help, would be just as disappointed as I was after a little while; we had picked five people who we thought would do just wonderfully and would fit in, but they said no. So I got the idea that we should get Shakow, himself, and suggested Seymour offer him the position of joint Lab Chief in Clinical Investigations, to get him to come. And since Seymour had the same difficulty I had in getting experimental psychologists, he offered the job to Shakow. He accepted it and built up Psychology in the Institute. I gave extra money to John Clausen, who was already there in Seymour's division, to stay.

And then we tried and tried to find a Senior Clinical Psychiatrist. I'd had my eye on David Hamburg for a couple of years, and finally, he agreed to come. Then, in 1954, I had gone to visit hospitals in Europe through the World Health Organization (WHO). I was sent to different places, and among them was Joel Elkes, in Birmingham. I was just fascinated that he had an idea about how one would bring together biology and psychology. He had a lot more background in chemistry

than I did, and so, I was hoping that he might come. Actually, in 1956, when he was here in that famous meeting that Jonathan Cole and Ralph Gerard arranged, Joel agreed to come to become chief of the laboratory that, tentatively at that time, we called Laboratory of Psychosomatic Medicine; it included Ed Everett, Irv Kopin, Bob Butler, who later became the Director of the Aging Institute, and Phillip Cardin, who had worked with the Wolfes at Cornell. Then, when Joel got back to England, where he was just setting up an experimental psychiatry unit, they said to him, "How can you do this? Here, we built a clinic for you, and now you're leaving." So, he wrote back to us and said that it just wouldn't be possible.

And then, one day, Seymour came in and said, "What would you think if I took that job?" I couldn't think of anything that would be better, and he brought Lou Sokoloff with him. Before that, on the same trip in which I'd met Joel Elkes, when I reached Paris, I found a letter from Ed Everett, who was the acting Chief of that group. He and Charles Savage were trying to find out how and where LSD work was done. Most of the work was on animals, and Ed had gone to the laboratory of Bernard Brodie to get some help finding out how LSD produced its effect. He wrote to me that there was a pharmacologist named Axelrod in Brodie's laboratory, who would be just the right person for our laboratory. Enclosed, was also a letter from David Shakow about a psychologist he met, so I wrote back from Paris to him: "go ahead offer them the jobs." This was my contribution to hiring Julie Axelrod.

TB: It seems that you brought together a remarkable team that set the foundation of the work at the Institute. It was also you who found Joel Elkes, who was to come, eventually, on board. You were also behind the meeting that was organized by Jonathan Cole and Ralph Gerard, in 1956, on issues related to clinical methodology in psychopharmacology.

RC: In 1957, I felt that we had reached the end of the beginning. David Hamburg was now the head of Adult Psychiatry and Fritz Redlich the head of Child Psychiatry. Seymour Kety was head of what we used to call the Laboratory of Psychosomatic Medicine and was to become the Laboratory of Clinical Sciences. Joel Elkes came back for a visit, in 1956-57, and said that now he could come. We had gone over to St. Elizabeths and I had talked to Jay Hoffman, who was the assistant director there, about getting a unit for him. Then Bob Felix and I went over to see [Winfred] Overholser, and he said, "how about taking a building?" I didn't want a building, but Felix says, "Wonderful," and so we set it up.

TB: So that was the building where Joel Elkes' Clinical Neuropharmacology unit was set up? RC: Yes. For the first two years, we used to have a dinner meeting once a month to talk about the program. I thought that we worked very well together. Then my old friend, David Bodian, came and got Seymour to go to Johns Hopkins and take Adolf Meyer's old job. David Hamburg went out to Stanford University and John Clausen went to the University of California at Berkeley, as Director of the Institute of Human Behavior. A year later, Seymour returned and said that he just couldn't see himself staying at Johns Hopkins and asked me about coming back. I said, "It would be wonderful if you did." So he came back. Then they got Joel Elkes a little bit later at Johns Hopkins, and Seymour went to McLean and Harvard in Boston.

TB: How did the departure of all those senior people affect your work?

RC: Actually, what happened was that the younger people, who stayed, took things over. After Kety left, we thought that we should offer Julie Axelrod the job, but after Julie said no, Irv Kopin took over. After Joel left, Floyd Bloom was there, and after Dave Hamburg left, Lyman [C. Wynne] was there and they took the jobs and did very well. I was sorry later to see Lyman go, but by that time, Bunney, Murphy, and Goodwin had begun working. Bunney had done some of the first clinical studies after Julie traced the effect of imipramine on the uptake of catecholamines, by applying these findings in basic research to psychiatry. The Institute moved ahead rapidly with biological research. And, then, I decided to leave. It was not that I had lost interest, but I no longer felt confident about my knowledge in making appointments. I'd been there for twenty-nine years at that time.

TB: You jumped way ahead to 1981. Could we get back to the late 1950s or early '60s?

RC: It was in 1957, as I said before, when we got that senior group together and I thought it was the end of the beginning. Everybody seemed to be deeply involved in the opportunity to do their research. We had an extraordinarily good relationship with Jim Shannon, who was the Director of NIH. And, of course, by the end of the 1950s, our horizon broadened. The year I joined Bob Felix, in 1952, NIMH's budget was something like twelve million dollars. Seymour had a million dollars of that and I had a million. Seymour and I were members of the senior staff and we would go over to his office to talk about the Institute, as well as our program. I remember during those early years, Dr. Felix went to Congress and Lister Hill said to him, "Dr. Felix, how much do you think you will come to ask us for in the years ahead?" And Dr. Felix said, "Senator Hill, I can foresee the

day when I will ask you for twenty-five million dollars.” He was just shaking inside. He hadn’t cleared this with Shannon, and he didn’t know what Shannon would say, but that was our horizon. And, gradually, our horizon spread. I thought we would have this small group of people, and if they stayed together for five years or longer, we would make a very solid contribution as a group. Later on, it became clear that we were going to have vast amounts of money, and with the increase of money, instead of having a relationship with each other, we were having relations with people in Europe and on the West and East Coast. The idea of groups working together really went by the wayside. We gave up on that and tried to support the productive groups that we did have; we’d follow where the results would go, in the direction that the research seemed to push us.

TB: I understand that with the money available in the late 1950s and early ’60s, activities grew rapidly in the laboratories and were extended to extramural programs. Could you tell us about the different kind of activities the Institute became involved with and about some of the outstanding laboratories and programs?

RC: Actually, it would almost be a question of saying what we didn’t do. After the Clinical Center had been open ten years, there were seven clinical directors, and at the anniversary, each director gave an account on 10 projects. And we unanimously agreed that Julie Axelrod’s was one of the most outstanding programs. This was before he got the Nobel Prize.

TB: So Julie Axelrod’s was one of the most outstanding programs. Didn’t you also have an important program on aging? Who was in charge of that?

RC: Jim Barron. And the psychopharmacology program also did very well.

TB: Were you involved in establishing the Psychopharmacology Service Center (PSC)?

RC: Not directly.

TB: But weren’t all programs in some way under your direction?

RC: Yes. I supported the Psychopharmacology Service Center, but I can’t say that I established it.

TB: But they had your support.

RC: Well, I supported it, and brought them together, and did things to try to keep them contented.

TB: The group you brought together in the PSC was instrumental in developing the methodology in clinical investigations with psychotropic drugs. They also played an important role in establishing the American College of Neuropsychopharmacology. And the group you brought

together at the Institute set the foundations of research at NIMH that was to lead psychiatric research during the second half of the 20th century. In the late 1960s, you became director of Behavioral Research at the Institute. Could you tell us something about your activities in those years, and especially, in the 1970s?

RC: It would be difficult to put into words my activities in those years, but by the end of the 1970s, as I told you before, I reached a point where I felt that I could no longer contribute to the further development of the Institute.

TB: Is there anything you would like to say, in general, about your experiences in the Institute during 29 years?

RC: I never had a moment feeling that Shannon wasn't completely behind me.

TB: Didn't you serve on some of the committees of the Institute, after you left?

RC: Fred Goodwin asked me to continue to serve on the promotion committee and I was very glad to do that until that committee was moved outside of the Institute.

TB: What did you do after you retired from the Institute?

RC: When I left the Institute, I was asked to come back to Chestnut Lodge as the Director of Psychotherapy, which I was sort of interested in doing. They were running into problems, because the younger doctors who were engaged in psychoanalytic training didn't want to give medications to their patients at all, and they thought that since I was a very senior person, I would be able to get them to use medication.

TB: Didn't you write a book in the 1980s on Frieda Fromm-Reichman?

RC: I wrote some papers, yes.

TB: You also wrote chapters in *Comprehensive Psychiatry* about manic depressive illness and schizophrenia. Are you still involved in writing papers?

RC: No. I felt that these last years have been difficult years for me. I can't hear well with my hearing aid, and I really can't go to meetings because I certainly can't follow. I can't hear well enough anymore.

TB: But during the 1980s, you were still active?

RC: Actually, for the 10 years after NIMH I was quite active. But really for the last four years, I'm not.

TB: Are you fully retired now?

RC: I really had to retire.

TB: You were born in 1909? So you are 91-years-old. You've had a very distinguished career that started in physiology.

RC: Ralph Gerard had a very profound effect on both my wife and me. I think my wife's sister also got a PhD and MD in his lab. I have not told you yet that my first wife, Mabel, died in 1972, after we'd been married thirty-nine years. But in 1974, two years after Mabel died, I married again, and I have been married twenty-six years now. Alice, my second wife, was in the Administrative staff at NIMH. My daughter from my first marriage is Professor of Pharmacology. She just presented a paper at a conference on cholecystokinin.

TB: So she is in the footsteps of her parents doing research. You did some early research in brain metabolism.

RC: One funny thing is that at the time when I was still directly involved in research and wrote my paper on hyperthyroidism and brain oxidation, they discovered that I had a carcinoma of the thyroid.

TB: When was that?

RC: It was in late 1956 or '57, something like that. I was fortunate that they were able to remove it. I really have had the experience of being a patient in the last years. After I retired from Chestnut Lodge when I was eighty-two, I had a good year and, then, I've had one thing after another.

TB: Could you tell us something more about your activities at Chestnut Lodge, after you left NIMH?

RC: My work was quite interesting. Of course, by the time I returned to Chestnut Lodge, the people I knew from before had left. David Rioch went to Walter Reed as Director of Neurological Research and was quite productive. Bob Gibson went to Sheppard Pratt Hospital. He was also President of the American Psychiatric Association at a certain point in time. Otto Will went to the Riggs Foundation, as Medical Director and Alfred Stanton became Medical Director of McLean Hospital.

TB: What have you been doing since you retired from Chestnut Lodge?

RC: In the last years, I've been reading, just reading.

TB: Is there anything else you would like to tell us? During the years you have been involved with many well know people. You also had some famous teachers. Would you like to mention some of them? You have already referred to Ralph Gerard.

RC: I had Frieda Fromm-Reichmann and Harry Stack Sullivan as my teachers, and what I remember is that when I finished discussing a patient with Frieda, I had some idea of what I should do next, and when I finished discussing a patient with Sullivan, I had some idea of what I had not been doing in working with the patient. While at the Phipps clinic, I had Adolf Meyer as my teacher and I can remember whatever Meyer said made a very deep impression on me. During my year at Phipps, five mornings a week, the whole staff attended a meeting that Dr. Meyer chaired; and each morning, one of us would give a report on our work with a patient. He always made the closing remarks. And I also remember that he sometimes invited us to his home for tea on Sunday afternoon and even for dinner once or twice during the year.

TB: So he had a close relationship with the students and residents. Did you have any contact with the late Horsley Gantt, while at Johns Hopkins?

RC: I had some contact with him.

TB: Did you ever take a course in administration?

RC: No, I worked my way up.

TB: In spite of that, you have become a most distinguished research administrator in psychiatry, receiving numerous awards for your achievements. Now, if my recollection is correct, during the presidency of Jimmy Carter, you became involved with the hostages in Iran. RC: Oh yes, I went over to Iran, and actually, I still hear from one of the former hostages, every Christmas. Two of the hostages have died since.

TB: You were involved with them in the capacity of a psychiatrist?

RC: Well, yes. I guess I was the most experienced, well, certainly pretty close to being the most experienced psychiatrist to go over. It was a very moving experience. They were an impressive group of men and women.

TB: So, you were involved with the State Department in those years?

RC: The State Department organized that very impressively. Before we went over, I knew whom I would see and had talked to their wives or parents and seen the letters that they had written home. Each of us had been assigned a particular person we would see. And, then, after we got there, each

evening, the medical staff got together to report what had transpired. We also had group therapy sessions. I thought the State Department did an extraordinarily good job on that.

TB: During the many years you have been involved with psychiatry, there were several paradigm changes in the field. You started in an era when psychiatry was dominated by Adolf Meyer's teachings. Then it was psychodynamics, and while you were at NIMH, biological psychiatry became dominant. Would you like to comment on that?

RC: Well, I would like to see the two, the psychodynamic and biological, brought together. It seems to me very sad that we aren't paying the necessary attention to the psychodynamics of people now that we have so very much more knowledge of physiology. I'm sure there are people who are trying to bring psychodynamics and biological psychiatry together. Eric Kandel is one of them. It seems to me that the lessons Adolf Meyer taught are still, in a sense, a guiding principle.

TB: What about drugs in psychiatry? When the new drugs were introduced, did you feel that they had a major impact on treatment?

RC: Yes, and I tried to follow the literature. By the way my wife's nephew played an important role in the discovery of Effexor (venlafaxine), one of the newer antidepressants. TB: Let me just ask one more question: What would you like to see to happen in the future in the field?

RC: I'd like to see psychodynamic therapy and pharmacotherapy brought together.

TB: On this note, we should conclude this interview with Dr. Robert Cohen, one of the most distinguished research-administrators during the second half of the 20th century, who was instrumental in setting the foundation of research at NIMH. Thank you, Dr. Cohen, for sharing this information with us. Thank you very much.

13. JONATHAN O. COLE

TB: I am interviewing one of the pioneers of psychopharmacology, Dr. Jonathan Cole¹⁵ for the Archives of the College. My name is Thomas Ban. Would you tell us where you were born and something about your education and early interests?

JC: I was born in Boston and raised in Cambridge. My father was a professor of Economic History at Harvard and was eminent enough to be head of the American Economic History Association and have a room named after him at Harvard's Baker Library. He was a somewhat austere man, who looked like he'd been to Oxford or Cambridge, but had in fact been raised in Haverhill, Massachusetts. My mother was of Pennsylvanian Dutch extraction, and on her side there was a fair amount of money, so we lived comfortably. I went to private schools and opted for science vs. history, at some point. I was in my last year of high school, during 1942, when Pearl Harbor occurred, and after graduating in the spring I went directly to Harvard, did pre-med, and got into medical school four terms later. I was sixteen when I got out of high school, because my mother made me skip the first grade. Without that, I would have died in the Battle of the Bulge. Instead, I was in medical school at Cornell, by that time.

TB: You knew by the time you graduated from high school that you wanted to go to med school?

JC: In the tenth grade, you had to choose whether you took history or science and I chose science. I was not well coordinated, as a kid, so I was not sure I could be a doctor. My first year at Harvard, I got an A in dissecting a frog brain and decided if I could do that, I could probably make it through medical school, despite critical noises from our housekeeper, who was sure I was a twatz and would never go anywhere. Actually, my father thought that too. My father was a good athlete and I was lousy.

TB: So, you went to Cornell?

¹⁵ Jonathan O. Cole was born in Boston, Massachusetts, in 1925. He received his M.D. degree from Cornell University Medical College in New York, in 1947. Dr. Cole completed his internship in Boston at the Peter Bent Brigham Hospital, and his psychiatry residency, at Payne Whitney Clinic at New York Hospital, from 1948 through 1951. After serving in the US Army during the Korean War, in 1953, he took a position as a Professional Associate to the Committee on Psychiatry at the National Academy of Sciences, in Washington, D.C., where he remained until 1956. He was Chief, Psychopharmacology Service Center at National Institute of Mental Health in Bethesda MD from 1956 to 1966, and then, Chief, Psychopharmacology Research Branch from 1966 to 1967. After a year at Temple University in Philadelphia, he became Superintendent of the Boston State Hospital, and then joined McLean, in 1973. He died on May 26, 2009 in Boston. He was interviewed in Nashville, Tennessee on July 22, 1999.

JC: Probably because I needed three people to represent me to go to Harvard and I didn't know three. At Cornell, they only required two. I applied and was accepted.

TB: Is there anyone who influenced your career choice?

JC: My mother made me read a fair amount about medical discoveries and in my teens, I read *Arrowsmith*, by Sinclair Lewis, and thought doing research and discovering cures would be wonderful.

TB: Books can have a great impact on people's lives.

JC: Yes. As a teenager, my best friend's older brother, after Harvard, took a job with Gillette, and the idea of finishing college and going to work for a big corporation struck me as creepy. Medical school, on the other hand, sounded orderly, predictable and secure. It was probably to avoid getting into unknown waters that I figured it would be best to get into medical school.

TB: How did you become interested in psychiatry?

JC: During medical school, I became interested in pharmacology. The department at Cornell was unique because Harry Gold was doing studies with placebo on anginal pain, insomnia, and the symptoms of arthritis, demonstrating that placebo had substantial effects on those symptoms. Then, I read Freud, while we were doing bad things to dogs in the physiology lab, and I wondered whether their response to what we were doing was due to their early life experiences. But, probably the most important factor that led to my decision was that my mother had bipolar illness that came on after a hysterectomy and spent the better part of her life in psychiatric institutions. So, I'd seen a lot of psychiatric hospitals. She would be wildly manic for a while, then very depressed. I thought during the first two years of medical school that I couldn't become a psychiatrist, because I hadn't majored in psychology, but by the third year, it became clear this was not true. During that same year, I had a very good teacher in psychopathology who gave some lectures at Manhattan State Hospital, where I got to see a fair amount of severe psychopathology. I also did one summer during medical school at MacLean's Hospital in Boston and greatly enjoyed having lunch with the psychiatrists. They were more fun to talk to than most people that I knew, so I decided that I wanted to end up in psychiatry.

TB: Did you do any research as a medical student?

JC: I mistreated some rabbits, as an experiment in pathology. I was interested in why some people have resistance to disease, whereas others don't. We chopped the skin of rabbits and injected the

protein to see whether you could create antibodies against it. I wouldn't say our research was a great success.

TB: I see. When did you graduate from med. school?

JC: 1947.

TB: You went straight into psychiatry?

JC: No, I did a year of internal medicine at Peter Bent Brigham Hospital in Boston.

TB: And after that into psychiatry? Where did you do your residency?

JC: At the Payne Whitney Clinic, part of Cornell in New York.

TB: I suppose psychiatry was psychodynamically oriented at Payne Whitney in those years?

JC: Yes and no. Our chairman was trained by Adolf Meyer. His attitude was you could only be psychoanalyzed during residency if you were screwed up enough to need treatment. I think he also thought that being psychoanalyzed would take you out of the hospital for about two hours a day for at least four days a week, which was bad for getting work out of the residents. He met with pairs of residents for three hours a day, one day a week, and went to the wards to see each of your patients. Supervision was extraordinary by present day standards. You hardly saw outpatients, and almost never saw a child, but saw a bunch of inpatients. You learned how to write five-page, single spaced, case presentations, which you had to give after the patient had been there about six weeks. You also learned how to comment on other people's cases.

TB: Did you do any research during your residency?

JC: You were supposed to present a paper. I read everything I could find on psychiatric reactions to ACTH and cortisol and presented a review, but I never could figure out anything useful to do in the way of a study.

TB: Who selected your topic?

JC: I'd seen some patients getting very happy on steroids, while I was an intern at Brigham with George Thom, who was an expert on the adrenal gland. We had a lot of Addisonian patients who were on cortisone that had just become available. I was also marginally involved with an ergot alkaloid, tested in hypertension, when I was a resident at Paine Whitney. It didn't work very well.

TB: Was it ergoloid mesylate (Hydergine)?

JC: No. I think it was a precursor or analog of it, but I wasn't really the one who was doing the study, I was more of an observer. My best friend in residency was interested in child psychiatry and when triiodothyronine (Cytomel) came along, he gave some to a five year old autistic child, who started talking for the first time.

TB: As a resident, what kinds of treatments did you use?

JC: The only treatment we had was ECT. I was impressed with it. I also did some sub-coma insulin, but I think in the wrong patients. We treated very disturbed patients and it didn't seem to me it did much.

TB: How was ECT given in those days?

JC: We took the patients to the ECT room, laid them on a firm mattress, put a big rubber band around their head with electrodes and zapped them, while everybody leaned on them so they wouldn't jerk too much. TB: Any other treatment?

JC: We used Amytal (amobarbital) IV for interviews and orally as a sleeping pill. We also had barbital (Veronal) for daytime sedation and that was about it. I remember a depressed man who told me, "Doc, when I get depressed, I need thirty milligrams of dextroamphetamine (Dexedrine) at night because I can't sleep and it makes me sleep like a log and I will get better." So, I gave him thirty milligrams of Dexedrine and he did sleep like a log, but he didn't get better.

TB: Anything else you would like to say about your residency?

JC: I remember that there was one social worker for a hundred and seven patients, so the residents had to take their patient's family histories. We were also trained to do the Wechsler intelligence testing. I'd also had a course on it in medical school so I got to be pretty good doing it.

TB: So you became expert in administering the Wechsler?

JC: Yes. By the way, Jolly West was a year behind me in residency and supervised me in hypnotherapy with a patient, which was fun. He had learned the technique in high school.

TB: You did hypnotherapy as well?

JC: I did that in only one patient, a pediatrician, who was a cross dresser. He had been unable to penetrate his wife after a year of marriage, but with hypnotherapy, she became pregnant in six months. Everybody was quite satisfied with the result.

TB: What did you do after residency?

JC: I went into the army. After basic training in Texas, I spent about 11 months in North Carolina, and then I was shipped out to Japan for a year. I spent most of the time in Fukuoka, in a small army hospital where I was the only psychiatrist. I met and married my first wife, a social worker, while in the army. During the time in North Carolina, I was working on an insulin coma ward.

TB: You did insulin coma treatment in an army hospital?

JC: I also gave lots of ECT.

TB: As a resident, if I remember well, you said that you used only modified insulin. Did that create any problem?

JC: I had a very good manual on insulin coma therapy from the Institute of Pennsylvania Hospital, which gave you a step by step description of how to do it, what to expect, and when to stop. And I didn't do prolonged comas, so the whole thing turned out very nicely.

TB: You think insulin coma worked?

JC: I remember only two cases where it did not work. One of them just got fatter and fatter. The other was an angry African-American, whom we could not get to go into a coma. He would get a little fuzzy and then start to scream, become excited and agitated, but never went into coma. We tried for about three or four weeks, then gave up. We did everything the manual suggested and a couple of other things. I remember those two failures, and ever since, I've been intrigued with insulin coma therapy. If somebody would give me a grant, I would try it again.

TB: You would?

JC: It's no better than antipsychotic drugs but whether they are the same patients, who respond, haven't been tested.

TB: Did you have any contact with Joe Wortis in those days?

JC: No. I met him later, but I never talked about insulin coma to him.

TB: He was the one who introduced insulin coma here, after meeting Sakel in Vienna. JC: Yes. He went to Vienna to be psychoanalyzed by Freud and came back with insulin coma.

TB: So your experience with insulin coma was positive but with modified insulin it was negative?

JC: Yes, but we used modified insulin mainly in disturbed schizophrenic patients on a female ward. I think it was inappropriate, in retrospect.

TB: What about drug therapy.

JC: We used barbiturates and I presume chloral hydrate was there.

TB: What did you do in the army hospital in Japan?

JC: I did outpatient consultations. It was very good for me, because I saw a lot of people who were illiterate, people with three or four grades of education that I hadn't seen at Payne Whitney. At Payne Whitney, if you couldn't play bridge or you didn't have at least a year of junior college, you were ostracized. So, I learned how to get along with people from the hills of Arkansas. There was some drug abuse in Japan by soldiers and I presume by the Japanese; I think they were using speed type drugs but we mistakenly thought they were opiates. It didn't matter because you got discharged from the army, no matter what you used. But I think I was diagnosing heroin addiction in people who were using methamphetamine.

TB: From Japan, you returned to civilian life to do what?

JC: I figured that I'd been at Payne Whitney so I'd go somewhere else. I arrived home to find a letter asking if I was interested in a job at the National Academy of Sciences, National Research Council in Washington, as a professional assistant and executive secretary to a number of research committees. This sounded interesting to me and I sent back a positive response. They interviewed me and hired me. So, I got onto the national scene. There were two committees I attended, advising the army on psychiatry and on stress. The stress one was run by George Thorn, who was chief of internal medicine at Brigham Hospital. There was also a committee on research about sex funded by the Rockefeller Foundation, a committee on alcoholism funded by the Licensed Beverage Industry, and the most important one, a committee on problems of drug dependence.

TB: When was this?

JC: It was from 1953 to 1956.

TB: Tell us what you actually did during the years you spent with those committees at the Academy?

JC: My job was to take minutes of meetings and to prepare, as secretary, the grant applications we received for the members of the committee to decide about them. It was very much like preparing the material for a NIMH study section.

TB: Could you tell us something about the Academy?

JC: The National Academy of Sciences was created by Lincoln during the Civil War, with the idea that it would provide independent advice to the government. At the time I was with the Academy, chlorpromazine and reserpine arrived on the scene and the Committee on Psychiatry

suggested I go to NIMH to find out what they were doing about these drugs. So I met with Seymour Kety, Ed Evarts, and a couple of other people and learned they were thinking of giving a grant to Ralph Gerard from the University of California to hold a conference on *How Do You Evaluate Drug Treatments in Psychiatry*. My appearance on the scene apparently convinced them to use the National Academy of Sciences as the agency to do the legwork in setting up the conference with Ralph Gerard, as principal investigator.

TB: Could you tell us something about Ralph Gerard?

JC: Ralph Gerard was an interesting man. He was a neurophysiologist, who had done major work in analyzing the national need for physiology. By the time the conference took place, he moved from California to Michigan and was trying to set up an empire there. He was more interested in getting a big grant for his studies than in the conference. He was strictly an advisor and wasn't actively involved in anything. He had a very quick mind but his wife had developed cancer at the time.

TB: Where did the conference take place and how exactly did it turn out? The topic was exciting.

JC: The conference took place at the Statler Hilton Hotel, in Washington, in the fall of 1956. It worked out reasonably well. We had about five concurrent sessions, probably unwisely, and we tried to record all the discussion. Then I had to edit it all. I ended up as senior editor, after having a power struggle with Ralph Gerard. I felt I did 80% of the work.

TB: It was, for you, a learning experience.

JC: Among other things, I learned that if you have federal grant money, it won't pay for coffee or doughnuts but you can get the hotel to charge you more for the use of their rooms and then they can include coffee and doughnuts, for free. I enjoyed finagling the system to a mild degree; it intrigued me!

TB: I see.

JC: It was while I was preparing for the conference meeting that Nate Kline and Mike Gorman testified before Congress that two million dollars should be appropriated to the NIMH to do a multi-hospital efficacy study of chlorpromazine and reserpine in schizophrenia. Their testimony included probably the first research design of a study ever presented in congressional testimony.

TB: Could you tell us something about Nate Kline and Mike Gorman? Who were they?

JC: Nathan Klein was head of psychiatric research at Rockland State Hospital in New York State and Mike Gorman was a reporter, who had written a book exposing public mental hospitals. I think they were representing Mary Lasker, who had a very rich husband and used her husband's money very effectively. She would help support people like Nate and Mike to lobby the congress, and then, she would give some money to people like Lester Hill, who was already in the House, to serve as catalyst to get the kinds of appropriations she felt were needed to treat various diseases. She was very wise about how to use soft money to achieve a great deal of leverage in getting money appropriated. And, it worked very nicely. Anyway, two million dollars got appropriated for the research but they needed somebody to run the program. As far as I could tell, I was, apparently, the only visible psychiatrist who knew how to review grants. And I was willing to move. All of a sudden, from first lieutenant in the army, I was offered a colonel's commission in the public health service. I accepted the job and moved to NIMH.

TB: When was that?

JC: After the conference.

TB: Could you tell us who participated in the conference?

JC: Representatives from the drug industry and representatives from academia.

TB: What was the title of the proceedings?

JC: *Psychopharmacology Problems in Evaluation*. It was published by the National Academy of Sciences and the National Research Council. I think I still have three copies at home. If the ACNP doesn't have a copy for their archives, I ought to send them one before they disappear. The book was not a vast commercial success. I think a thousand copies were printed and about a hundred were left, which the academy gave to me to get rid of. I've given them to various people since.

TB: I have, actually, a copy of that conference in 1956. We had chlorpromazine and reserpine by that time, but we didn't have imipramine and iproniazid, as yet.

JC: Imipramine was certainly not on the market; it became available two years later. Meprobamate (Miltown, Equanil) was already on the market and was selling like hot cakes. Frank Berger, having discovered it, received a lot of publicity at the time. FDA did not require efficacy for a drug to be marketed in those years, only safety. In 1956, there was a conference on meprobamate at the Waldorf Astoria in New York.

TB: I think the Huxley brothers, Aldous and Julian were there.

JC: I don't know. I wrote my first formal paper for that meeting and I got paid two thousand dollars.

TB: What was it on?

JC: It was a historical review of treatments.

TB: You said it was your first paper?

JC: Yes. The only thing I had ever done before at the Academy was a bibliography on fatigue.

TB: Could you tell us more about that review?

JC: I reviewed some of the recent papers on chlorpromazine, as well as old treatments, but not only pharmacological treatments. One of the most outrageous treatments was based on the assumption that psychiatric illness was due to infection and the treatment was getting rid of anything that might harbor an infection. They pulled all the teeth, cleaned out the sinuses, and removed the colon.

TB: The colon? Where was that done?

JC: At Trenton State Hospital. They had a very high discharge rate; people didn't want their colons removed. I covered the treatment of neurosyphilis with penicillin, comparing it with malaria treatment. I also got into literature on the treatment of parasites, and reviewed insulin and electric shock.

TB: What about treatment with vitamins?

JC: I didn't come across much because that didn't get written about. I did touch on it later through Abe Hoffer.

TB: I was thinking of nicotinic acid in pellagra and thiamin in the amnestic syndrome.

JC: They used to say, "if you find a nice cure for something like pellagra with Vitamin B and penicillin for cerebral syphilis, those patients get taken over by general medicine and you never see them again."

TB: We are in the late 1950s, when you got to NIMH. You certainly were the right person for the job.

JC: I was handy and they couldn't think of anybody better, who would come on such short notice. I also came with a good deal of humility; wasn't sure what I was going to do. I was helped in the first year by Sherman Ross, who was professor of psychology at the University of Maryland. He

had the longest and most heterogeneous publication list that anybody had ever known. He had one paper called, "Gorilla-Gorilla-Gorilla" and at the other end he had papers on industrial psychology, on psychometrics, and even a paper on coca-cola. He never got a chairmanship because he wouldn't focus on anything. But, he knew a great deal and was on sabbatical. So, I had him as a consultant to help me set up a psychopharmacology program and he proved very useful, both in teaching me research and recruiting staff to help run things.

TB: Could you name them?

JC: Sy Fisher, Marty Katz and Dean Clyde.

TB: When did they join you?

JC: Some of them came in late 1956.

TB: And what was your mandate, evaluation of new drugs?

JC: I didn't feel capable of that. The first year was spent recoding existing grants to make them look like psychopharmacology. We ended up with a list of grants, like Carl Pfeiffer's, a big sloppy grant, mainly about epilepsy, but there was a section in it about whether it would be interesting to give schizophrenics a sedative and see whether it worked. We had a grant that dealt with carbon dioxide, which was a biological treatment by a basic scientist at Penn, who was studying the effect of carbon dioxide on the brain. Scrounging around, recoding things that might just barely have a possible role in psychopharmacology, we came up with about \$800,000 worth of stock to report to Congress by December. I turned out to be good in writing reports to Congress; so throughout my time at NIMH, I did what one might call the science writing, I wrote the reports for congressional inquiries and that sort of thing.

TB: You wrote the reports?

JC: I wrote the reports. And then, in July of 1957, Jerry Klerman came for two years on a military draft exemption. Those were the days when you had to do two years in the military. If I would have been wise enough myself, I could have spent my two years in NIMH, rather than with the army in Japan; although, it was probably good for my education to be in the army. So, Jerry came and I hired him; he was obviously very good. Then I hired Sol Goldberg, a psychologist, and the three of us planned the nine hospital collaborative study, which did what Nate Klein had in mind, comparing promazine, thioridazine, fluphenazine, and placebo in newly admitted, first or second admission, patients with schizophrenia. It is interesting to compare what we did then, and how we

do things these days. We had enough money to do the study, so we went to the APA meeting that year and solicited people to write an application if they were interested and capable of doing a study, which would require admitting one hundred and twenty patients with schizophrenia in two years. There was only one application that was not approved.

TB: Do you remember the participating hospitals?

JC: DC General, Springfield State Hospital, City Psychiatric Hospital in St. Louis, Rochester State Hospital, Manhattan State Hospital, and the Payne Whitney Clinic. We also had a hospital in Danville, Kentucky, The Institute of Living, and Stonybrook and one of the private hospitals in upstate New York.

TB: So, the study was designed by you and Gerry Klerman?

JC: Together with Sol Goldberg. And we also appointed a review and an advisory committee.

TB: The primary criterion in the selection of hospitals was to have enough schizophrenic patients?

JC: Yes, but they had to show they could organize and run it well. It was interesting that dropout rates were zero in hospitals where the superintendent was the principal investigator. One of these hospitals was in Rochester, another in New York, a third in Danville and Springfield State Hospital. In these hospitals, there were no dropouts, for any reason, during the six weeks of the study.

TB: What was the overall dropout rate?

JC: It was about twenty-five percent. The highest dropout, fifty percent, was at the DC General Hospital, in Washington, followed by the City Psychiatric Hospital, in St. Louis, Missouri.

TB: Was the diagnosis based on DSM-II criteria or simply a clinical diagnosis?

JC: We had no diagnostic instrument, but we could go and look at the Lohr scale data for these patients. John Davis still has the data on tape, because he reanalyzed it about twenty-five years later.

TB: Wasn't the Lorr scale the main assessment instrument in the study?

JC: The Lorr and the Burdock scales. We probably also had a global improvement scale, but I can't remember. We never knew what to do about side effects. We recorded them, I can't remember how.

TB: Do you think that in some of the patients the diagnosis might have been wrong?

JC: I presume, in retrospect, that maybe a third of patients were schizoaffective psychoses, or at least ten percent were psychotic patients with mania and probably a few amphetamine psychoses were also in there.

TB: How did you decide about the sample size?

JC: We had statisticians at NIMH and asked them how big our sample should be. The answer we received was, and I quote, "As many as you can get." We did not do any estimation of the effect size or anything like that.

TB: I assume by that time you had quite a bit of experience yourself, with chlorpromazine and with some of the other phenothiazines.

JC: No, I didn't.

TB: You did not.

JC: I'd had one anxious lady I saw before I went to NIMH, and she was complaining of stiffness in her knees. She thought she was getting arthritis. It turned out she was on reserpine for her high blood pressure and had early Parkinson's from it. That was about as close as I got.

Of course, I had been to a lot of meetings and talked to a lot people.

TB: You didn't have a private practice in the years when chlorpromazine and reserpine were introduced?

JC: No. I went to meetings, talked to people and guys on the advisory committee with experience. I think that worked reasonably well.

TB: Who was the statistician involved in the analysis of your collaborative data?

JC: I think it was Dean Clyde. He had experience with computers back in the days when we were key-punching the data. The kind of thing I would do is to make sure the contract got to people; the study was set up right and looked okay.

TB: Could you say something about the results?

JC: The three drugs were usually better than placebo. We had about eighty-five dependent measures, and on none were any of the drugs significantly different from one another. It should have been a couple, by chance alone. We played around with predictors of improvement and found that disorganized schizophrenics did better on chlorpromazine and paranoid patients on fluphenazine, but in a second study it didn't replicate. By and large, the history of trying to replicate predictors in drug responses has not been too successful.

TB: Remind me, what was the duration of the study?

JC: Six weeks, if my memory is correct. It wasn't longer than that. We then did a twenty-six week study, in which we used the three drugs but no placebo with a couple of other hospitals included, and what we found was that there was not much further improvement after the thirteenth week. And, our impression was that negative symptoms did about as well as positive symptoms.

TB: If my recollection is correct, in one of the first reports, it was suggested that negative symptoms respond to drugs only, whereas positive symptoms are placebo prone.

JC: The total improvement was better in the positive symptoms, if you included everything, but the drug placebo difference was greater in the negative symptoms. We went on and did a high dose vs. low dose study. We tried to figure out what a high dose of chlorpromazine should be and we never got a clear answer. We ended up with two times 2000 mg as a high dose, but investigators would say things like, "I have one patient up around 5000 mg a day and he begins to look better." But two times 2000 mg seemed like a reasonable upper level to me.

TB: Could you tell us about some of the other programs of the Psychopharmacology Service Center?

JC: We were given enough money to do a lot of things. One of the things we did that worked very well was the Information Center in Madison, Wisconsin.

TB: I see. Could you give some background to the Early Clinical Drug Evaluation Units, the ECDEU program?

JC: In traveling around, I encountered a lot of places, mainly state hospitals, but also at some universities, where people were getting funded by industry for a few months or a year or two and then the funds would drop off, making it hard to retain good staff or keep an organized program. It seemed it would be reasonable to give some centers sufficient support for a structure that would keep them going for several years and give the investigators a chance to do some studies of their own design. I remember Heinz Lehmann telling me he wanted a cost accounting study to be done for a Smith, Kline & French study because he thought that if SKF paid for the whole thing, it would have been three times what they actually paid. They were getting a lot of support from the institutions where the investigators were working. So, I suggested to the head of NIMH, who in turn proposed it to Dr. Shannon, the head of NIH, to set up and fund the ECDEU program.

TB: We are talking about 1960, approximately, right?

JC: I think that's about right. It came after we set up the nine hospital study and got it running. We had a little breathing room and the next thing was the ECDEU program. It went quite nicely, as Henry Brill, Deputy Commissioner of New York State had already created a number of research units in state hospitals. Sidney Merlis was already at Central Islip and George Simpson at Rockland State.

TB: George Simpson was already working with Nate Kline and I think Don Gallant in New Orleans with Bob Heath.

JC: Heath was a remarkable man. He went from Columbia to Tulane, so he could put wires in people's brains, things they probably wouldn't let him do in New York. He was clearly interested in neuropsychiatry, and especially, what the pathology was in schizophrenia. He trained excellent psychiatrists, who now staff the Louisiana State Hospital system. So, he ran a good clinical program, trained excellent people, while doing his oddball research. I think he was deceived by his research assistants; they kept recording figures that didn't quite work out. People went down to site visit and they couldn't find the data. It was all very strange. My guess was that he was so charismatic that his research assistants found things to please him. It all fell apart, under scrutiny. But, Don Gallant, the guy who came in with him did very nice work.

TB: You also had Pierre Deniker in the ECDEU group.

JC: From St. Anne's in Paris. We got permission for a few foreign grants, including David Wheatley's. He was doing studies with general practitioners in the UK. There was a major convulsion at NIMH, when it turned out that Dave Wheatley's was a for-profit foundation. I can't remember how we resolved that. I think we finally stopped the grant. For three or four years, we were funding him, assuming he was non-profit.

TB: The ECDEU program was certainly growing very fast. Would you like to say something about other studies and activities of the Center?

JC: We tried a study in outpatient anxiety and did a series of small studies, mainly at Hopkins and with Karl Rickels in Pennsylvania giving chlordiazepoxide (Librium) to anxious outpatients. Someone had the idea that if you gave patients a drug which caused noticeable side effects, it would have therapeutic effects. It turned out that it worked exactly the opposite way. Rickels worked with medically ill people who were dumped on psychiatry by medical outpatient clinics

and when he gave them a dry mouth on top of their troubles, they thought that was a major imposition.

TB: Then you did a collaborative study in depression?

JC: We did a seven hospital study of inpatient treatment of depression. They were patients who'd failed on tricyclics as outpatients so I expected to find, if they took tricyclics as inpatients, they might do differently. We really had to analyze the data in various fancy ways to even show that imipramine was different from placebo. By only taking the worst half of the patients, we could show that it was. We opted for a dosing regimen, where the dose went up to about the fourth week and then came down in the sixth week. We didn't yet understand you ought to get the dose up and stay there for a while. And we'd gone wild on metrics. We had about twelve different rating scales we factor analyzed. By the time we got to that point, I think, we had data poisoning. The findings of our study were published, but it was not a great success.

TB: You said that there were many rating scales used.

JC: We had the BPRS and several other scales, including one that Al Raskin developed. I can't remember the scales we used anymore. We accepted anybody for that study who was depressed psychotic or not; we didn't discriminate. Some of the findings were sensible, e.g., that agitated patients got better on chlorpromazine, whereas unagitated patients got lethargic. And only in the sicker half of the patients, in the more endogenous non-alcoholic patients, could we pick up an effect.

TB: So, findings were not spectacular.

JC: Weren't spectacular. Then, Bob Prien joined us and he was running a lithium vs. chlorpromazine study in bipolar patients; that worked out quite nicely in retrospect.

TB: When did Bob Prien get into the picture?

JC: Around 1960. He was a psychologist who was working for the drug company, Lakeside. He came to work for Ron Bonato at George Washington, in the Biometric Laboratory, and we ran the lithium, chlorpromazine comparison in bipolar patients.

TB: Is there anything else you would like to add?

JC: Marty Katz and I did a study with LSD in prisoners at an institution in Maryland, where they send violent people.

TB: Then, in the mid-1960s, you left NIMH?

JC: In 1967, two things happened that blew me out of the NIMH. They turned down the offer of St. Elizabeths' to give me a research ward. If I had been given the research ward or the responsibility for research on drug addiction, I would have stayed.

TB: Where did you go?

JC: I accepted the position of Medical Superintendent at Boston State Hospital and spent a fascinating five years learning all about community mental health and open door policy.

TB: Those were the years of deinstitutionalization.

JC: We were doing quite well with our discharged patients, so it was not a bad program. I was convinced that for some patients, the hospital was a better place than the nursing home to get help. I played for awhile with the idea of how you could measure quality of life in nursing home and hospital inpatients who, wherever they were, said everything was fine because they hated change more than anything. I would rather have kept the hospital going even if they wanted to close down hospitals. I would rather close other places and transfer more patients to us to take care of. We closed our medical research facility and started using the public health hospital instead.

TB: What would you have done actually if you had your way?

JC: I would have stopped discharging patients. I would have liked to think about who we wanted to admit and who we wanted to discharge. I would have liked to decide who we could help. That's the crucial question we never found an answer to.

TB: I see.

JC: I began to feel that my flexible administrative style plus the lack of any liability insurance for my deeds as Superintendent were going to get me into trouble sooner or later. The business manager of the hospital used to complain that we fed twice as many people at lunch time than we did any other time of the day. A lot of our discharged patients would come back and mix with the current patients and eat lunch in the hospital. I began to have cardiac symptoms, probably psychosomatic, and decided to take the Chairmanship of Psychiatry at Temple University, in Philadelphia, for a year.

TB: So you went to Philadelphia.

JC: For a year; but by the end of the year, Temple did not look as good and I was offered a job at McLean's back in Boston.

TB: You are still at McLean. Are you still active?

JC: I am seeing depressed patients and occasionally other patients, in consultation.

TB: We have to wrap it up now, but I have one more question. While you directed the Psychopharmacology Service Center, you were in a position to influence the development of the field. Did the field move in the direction you would have liked to see?

JC: I would have liked to see clinicians and basic scientists getting closer, to see some kind of closing the gap between them. I'd always felt both, clinicians and basic scientists, should be supported. I was always worried that the basic scientists were studying A, while clinicians were observing B. I think we have made some progress in that direction. I am impressed that people like Steve Hyman, who directs NIMH currently, has a good command of both ends of the spectrum.

TB: So, you seem to be pleased to see what is taking place. On this note, we conclude this interview with Jonathan Cole. Thank you very much Jon, for coming to Nashville for this interview.

JC: Thank you Tom for helping me. Thank you, Oakley Ray for asking me to be interviewed again.

TB: Well, thank you for answering all these questions.

14. THOMAS B. COOPER

TB: This is an interview with Thomas Cooper¹⁶ for the Archives of the American College of Neuropsychopharmacology. It is December 9, 2003; we are at the annual meeting of the College.

My name is Thomas Ban. Please tell us where and when you were born, and about your education?

TC: I was born in England, in 1935. After my initial education, which was in medical laboratory technology, and later, in biochemistry and biochemical pharmacology, I came, in 1960, to the Rockland Research Institute, which later became the Nathan Kline Research Institute. I came for two years. Forty-two years later, I am still here. I came at a time when psychiatry was on the brink of moving away from psychoanalytic theory towards a more biological orientation. Nathan Kline was one of the very few people who believed in the biological aspects of psychiatry. As a young neophyte, for me this was a given, and it wasn't until I had been to meetings about two or three years later that I realized we were either on a cutting edge or way out in left field, whichever way one wants to look at that. It was a marvelous time in research because there was a lot of money and not too many people trying to get it. To give an example, Jonathan Cole telephoned me in 1964 and asked would it be possible for me to take my first grant three months early. He would fund it for the extra three months because they had to get rid of some money in a short time. My naiveté was such that I said I would have to ask Dr. Kline whether this was acceptable. Jonathan Cole, with that marvelous belly laugh of his, said, "Well, I think it will be." So, I duly went to Nathan Kline and got a quiet smile with an affirmative that I could certainly accept the money ahead of time, especially the extra money! That was my introduction to grantsmanship. I must tell you from then on, it has gone downhill steadily. It is much harder to get grants. But that was how I came into psychiatry. Rockland Research Institute was a program within a major state institution. When I arrived, there were 9,000 patients on campus. There is now something like 380. Unfortunately, as we all know, there are still patients who are on the streets and homeless. But the bottom line is that the hospital campus on 680-odd acres is now very small but the Nathan Kline Research Institute still thrives there.

¹⁶ Thomas B. Cooper was born in South Shields, England in 1935. After training as a biochemical pharmacologist in England, he started at the Rockland Research Institute, which later became the Nathan Kline Research Institute, in 1960, and has continued his research there and also at Columbia University throughout his career. He was interviewed in San Juan, Puerto Rico on December 9, 2003.

TB: You came in 1960?

TC: Yes.

TB: How did you get to join Nate?

TC: The Institute advertised a position in England. I picked this up and was interviewed by George Simpson. I lived in Newcastle, in the northeast part of England. It's a good place to leave in terms of the climate. So I wasn't unhappy when I came to New York and saw sunshine. George Simpson apparently liked what he saw, I was offered the job, and came over. George was interviewing me for the job at the Institute with a Dr. Cranswick, who turned out to be an Australian. When we arrived in the US, in March, in fourteen inches of snow, we were met by Drs. Simpson and Cranswick, the latter wearing an open shirt, a pair of shorts, sneakers, and no socks! Frankly, I didn't know whether I should turn around and go straight back! But he turned out to be a delightful fellow, a psychiatrist and endocrinologist, and bright as could be. So, I was recruited by Kline, and gradually over the years became extremely friendly with him. I had, and have, tremendous respect for what he did. I was very lucky.

TB: Could you say something about your work at Rockland State after your arrival? TC: When I arrived at the Nathan Kline Research Institute I lived on the campus with my wife. We were directly involved with patients, who lived in the same building where we worked. Nate Kline (and I think he was absolutely right about this) said that young researchers should be exposed to who they were studying to see what a patient's life and their illness was like. I came to the Nathan Kline Institute to work on the thyroid physiology aspects of mental illness. Dr. Edward (Ted) Cranswick had a penchant for building his own multiple channel radiation detector equipment, long before such equipment was available for routine clinical use. In that context, we had contact with patients over many days, when they were given small doses of radioactive iodine, and we looked at uptake and turnover of compounds produced by the thyroid and the effects of psychotropic medication on these measures. We also had close contact with the patients in simple things like collecting urine and making sure blood collections were correct. That was my first exposure to this type of patient and population. There were many other basic scientists and psychiatrists working at the Institute, and we all worked in close proximity to the patients. There was Dr. Vestergaard, a psychiatrist and endocrinologist interested in steroids.

He developed methodology for measuring steroids that was way ahead of its time. He was one of the first people, who had an almost totally automated liquid chromatography system for urinary steroids across the whole spectrum. He would spend hours and days working with patients, collecting consecutive 24-hour urines over months, and in some cases, several years.

There are many amusing stories about that. We had some patients who didn't really want to have their urine collected. We had others, who collected urine and put their ball point pens in the urine. I remember a patient, who was extraordinarily bright. He came in one day with a bottle that was full. The urine was a dark blue in color, so Dr. Vestergaard asked "What have you done to this urine?" The patient reared up imperiously, and said, "Dr. Vestergaard you are the chemist." There were many, little vignettes like that. I found it an enjoyable and productive area to work in, simply because I knew everything that was going on. We had meetings regularly. Nate Kline joked, that he traveled a lot, and when asked, "Who does all the work when you're away," his reply was, "Exactly the same people who do it when I'm there." And, this was truly his attitude. If he thought you were good enough, he left you alone, to get on with whatever you wanted to do. I found that terrific.

TB: So you worked after your arrival, in the thyroid laboratory. Weren't you in charge of that lab?

TC: I took over the thyroid laboratory, in 1964, because Dr. Cranswick died. He had a cardiac infarction and died six weeks later.

TB: He was in charge of the thyroid lab before?

TC: Yes. After I took over, George Simpson and I worked for about two years on the differences Ted Cranswick had observed and because we developed the capability to measure total iodine in plasma, we realized that a lot of the findings we had were due to the patient's high iodine diet. Because of that their thyroid function looked as if it was reduced, when in actual fact, it was not. We found that there were no major changes in the function of the thyroid in these patients. During that time, we developed methods for iodine analysis, which in the early 1960s, were very difficult assays to do. We were paying a commercial firm something like \$25,000 a year to do the assays, and at that time, I was earning about \$6,000 a year. So, I suggested that if I did the assays and split the \$25,000, I would be ahead of the game. After Ted Cranswick's death, which was a tremendous loss, Nathan Kline first made me acting director, then after I gave a talk about the

thyroid findings, he suddenly said, “OK, you’ve got this department. This is your lab. Go ahead and work with it.”

TB: What were the initial findings?

TC: The finding initially by Dr. Cranswick was turnover of the iodine in the thyroid gland was very slow in chronic schizophrenic patients. We did these measures every three months, on and off drugs. The drugs, in those days, were not as esoteric as they are now. Then we found that the hospital supplemented the diet with iodized salt and this created the misrepresentation of low thyroid function, when in actual fact, a lot of iodine was going into the gland. We didn’t understand the low activity we had found until we were able to develop analytical methods which measured total iodine, and then, we realized that these patients had enormous amounts of iodine circulating in their blood, and therefore, the uptake of the radioactive iodine was extremely low. So the results after a number of years work were really negative and there were no major thyroid abnormalities in these patients. The rationale for looking at the thyroid, in the first place, was a syndrome called myxedema madness, in which patients who had major thyroid abnormalities could manifest psychiatric symptomatology. This led to the idea that perhaps there was some basic thyroid or endocrine abnormality in schizophrenia, which we could examine.

TB: Didn’t you study periodic catatonia?

TC: Per Vestergaard was working with periodic catatonic patients. Nathan Kline brought together a group, which designed a study protocol to examine the interaction between endocrine systems and psychotropic drugs in schizophrenia. We joined this group and studied thyroid drug interactions. The periodicity in steroid output collected over many years in a relatively large patient cohort was published, but in my opinion, never got the attention it warranted

TB: Did he try to follow up Gjessing’s findings with thyroid administration?

TC: Yes. He was inspired by Gjessing’s work and followed that for a very long time. The work clearly showed that there were patients who were periodic catatonics. He tried interventions; one that worked was using cortisol. But most of the treatments he tried, did not work. Catatonia nowadays is something that a lot of young psychiatrist’s claim they have never seen. But to see it, at that time, was quite devastating.

TB: We are talking about the 1960s.

TC: Yes. Slowly, in the thyroid lab, we began working with Dr. George Simpson, who had an early clinical drug evaluation unit. We started looking at psychotropic drug levels and drug metabolism in schizophrenia. First, in the urine, because that was all we could look at; then gradually, as gas chromatography, liquid chromatography, and mass spectrometry became available, we were able to develop methods of sufficient sensitivity to look at tissue and blood levels of the drug and many of the metabolites. Now, I'm jumping forward a 20-year period. At the beginning, we were able to measure very little, and progress was really slow.

TB: So you started with measuring urinary metabolites of psychotropic drugs?

TC: This is just because we had the metabolites that were present in large quantities quite often.

TB: Could you tell us the drugs you studied?

TC: Phenthiazines, and antidepressants, a little later. We didn't get much work in antidepressants until the 1970s, mainly because of the patient population. It was only when we were doing work with Dr. Kline and Dr. Simpson outside of the hospital that we started looking at not just chronic depression, but acute depression.

TB: So, first, you worked with antipsychotics?

TC: Yes. The findings are well known now, but then were very surprising. Most people, at that time, thought that if you looked at dosage of a medication and outcome that was all you needed. The initial findings were very clear that patients metabolize at different rates. For instance, with the phenothiazines, we confirmed that there was a 30 to 40 fold variation in the metabolism of the compound; that one patient, given 100mg, could have 1ng per ml in the plasma, and another patient, given 100mg, could have 200 or 300ng per ml at the exact same time point and dosage. It became very clear that to simply say that 300mg or 600mg of chlorpromazine was an adequate dose was totally inaccurate, because the patient can metabolize the drug extensively in the gut before it ever reaches the systemic circulation. This was, at that time, a major finding. We also were able to show that there is a very strong correlation between the total concentration of the drug in plasma and brain. What is surprising is that these drugs were highly bound to protein. Yet, if we looked at brain levels in animals and in humans, we found that the brain levels were 20, 30, 40 times higher than the plasma levels. So, even though the drug was highly bound, it moved across the blood-brain barrier very quickly, and the bound material became free very quickly. So, we had equilibrium between brain and plasma. That data has held up over many years. We have the

glorious images of PET now, and clear data which show that if you look at the plasma level of haloperidol, and the occupancy of the D₂ receptors in the living human brain, the correlation is extremely high. In collaboration with Adam Wolkin, et al. at NYU, our first experiments involving PET demonstrated that D₂ occupancy reaches its peak at about 15 ng per ml of haloperidol, and that is exactly what one finds in terms of clinical efficacy. You get very little benefit from going higher than that, and doubling the dose doesn't give double the efficacy, but increases the side effects. The development of these assays has been a good part of my research life and experience. I don't quite know how that developed. I really don't. We got more and more interested as we went along. I think this is where I owe Nathan Kline a great deal; he believed in the interaction between clinicians and so-called basic scientists and I benefited from that. I do a considerable amount of work with many collaborators across the country, and indeed in other countries. I think it benefits me and them. We bring to a study a level of laboratory expertise, which many clinical units could not develop because it is too costly. Clinical studies are very time consuming, and therefore, one institution can only focus on a limited group of patients. To function as a core laboratory for several clinical research centers increases our scope and is intellectually stimulating. This, I find, very satisfying.

TB: When did you start to work with antidepressants? Didn't you start sometime in the 1960s?

TC: We started working with antidepressants in the late 1960s. At that time, the methodology was extremely crude. Many people were trying to measure these compounds and, I must admit, not very successfully. If one looks at some of the early data, reports were of imipramine being present in microgram per cc. amounts, where in actual fact they are 1,000 times less. This was due to the non-specificity of the methodology. As things progressed, we got into gas chromatography with nitrogen detection, and found that we could quantify exactly how much imipramine, and metabolites were present in plasma. The nitrogen detector came out, in 1974, and we were fortunate because we got the first nitrogen detector in the country. We read about this in a paper, telephoned the company who built the machines, and they said they had just one, which we could have, provided we bought it, which we did. That was one of the great moments in my career in terms of instrumentation, because I was suddenly able to look at a chromatogram and see that this simple detector resulted in a 40 to 50 fold increase in sensitivity. I also had far more specificity in that most compounds which don't contain nitrogen are not detected by this system. Thus, the

peaks on the chromatogram contained nitrogen, e.g., imipramine and metabolites, and all other compounds gave little or no signals. That started about 1974, and from then on, we continuously developed methods for the antidepressants, both first generation and second generation. We've developed methodology for the phenothiazines, the new antipsychotic drugs and blood, spinal fluid, and tissue assays of all of these compounds.

TB: What do you consider your most important finding?

TC: With antidepressants, the strongest findings are with imipramine and nortriptyline. If you have imipramine plus the metabolite, desmethylimipramine, which is also an antidepressant drug and the sum of these, is around 200ng, which is the optimal therapeutic level. With less than that, when the patient is not responding well, raising the plasma level can increase the number of patients who respond by about 20%. There are, however, patients who do not respond to imipramine no matter what the blood level. Glassman and Perel were the first group to describe this threshold of 200–220ng per ml. It is worthwhile noting that this helps understand why some patients require a very large amount of medication, which physicians may be reluctant to give without knowledge of the blood level.

TB: What did you find with nortriptyline?

TC: Nortriptyline seemed to have what we call the inverse tea cup or U-shaped curve, a level above which you must reach to get clinical efficacy. As you move further on, you reach the point at which clinical efficacy deteriorates, with toxicity coming in, and then full toxicity if you go high enough. The Scandinavians were the first to demonstrate that nortriptyline is the only drug where you have hard evidence that if you get a patient up to about 80 to 100ng of nortriptyline, you are in the optimal situation for that particular patient. The range varies from different findings but is about 50 to 150ng. If you get up to around 180 to 200ng, you start getting toxicity and side effects, including cardiac effects. So, with imipramine, we had a lower threshold, but no apparent upper threshold except obvious toxicity. With nortriptyline, we have a lower and an upper threshold. This meant to me that blood level monitoring really had a place in treatment in psychiatry. We went on to the antipsychotics. The Scandinavians did an enormous amount of work on chlorpromazine, showing that lower dosages seemed to be as efficacious and had fewer side effects than high doses. To give examples of that, when I first went to Rockland, to see a patient receiving even 2 grams of chlorpromazine a day was not unusual. You might see a little old lady, who

weighed 50 kilos, taking that much chlorpromazine, who didn't bat an eyelid. We would draw blood on patients like this and find their levels were extremely low. It turned out that chlorpromazine is one of those compounds which, like many others, will induce its own metabolism. The gut metabolism can be induced to an extent that you virtually don't have any chlorpromazine present in the plasma, and therefore, in the brain. So this little old lady we're talking about, in actual fact, was getting a very small dose of chlorpromazine. She was simply metabolizing it so fast that it was probably useless.

The classic example we have of that is a patient of George Simpson's, who was on butaperazine, in the middle 1970s. No matter what was given, the patient responded for a week and then the response disappeared. In frustration, he was put on the butaperazine, and we did kinetics, collecting something like 10 bloods samples over a 48-hour period. These showed a very nice kinetic curve with the peak at about three hours. Eight weeks later, even though his medication had been increased to twice the maximum permissible dose, he had no clinical effects whatsoever and deteriorated. When we did a second loading dose, we couldn't find any butaperazine. We looked at similar kinetics with chlorpromazine and found exactly the same thing. But when he was given intravenous drug, he had a profound effect immediately. So getting medication past the gut enabled him to benefit. This patient has done well on a long acting intramuscular injection that's not metabolized by the gut. But every time he is given oral medications, it doesn't work.

TB: Did Hilary Lee work with you on these projects?

TC: Hillary Lee worked with George Simpson and me. She worked with you, also, before that.

TB: What happened after George Simpson left the Institute?

TC: There was the usual period when I thought maybe I would go and work with him but that didn't happen for a variety of reasons. One, he was working in California, and the California housing costs were astronomical. So I decided I could still work here. Nate Kline always had been extremely supportive. We had become much closer in our relationship over those years, but at the same time, I was recruited by Columbia University to go to the department of psychiatry, when Edward Sachar had taken over as Chairman, and Don Klein was there. Nate agreed to this. I didn't want to leave the lab, because I had a lot of people working with me, and many were women

with children who would not have moved. So a deal was made that I would work part-time at Columbia and part-time at Rockland and, in fact, that still exists today.

TB: When did you start to split your time between the Nathan Kline Institute and Columbia?

TC: In 1980. Nate agreed to all of that, and then unfortunately, died in 1981. I started doing collaborative work at Columbia, which opened up a whole area in which I had not been previously involved, namely child psychopharmacology, working with Drs. Greenhill and Shaffer. That has been particularly productive because we have looked at methylphenidate and methylphenidate enantiomers. In fact, our lab has done all of the kinetic work on the enantiomers, which has demonstrated that the D-methylphenidate enantiomer can be given to patients at half of the dosage of the racemic mixture with comparable clinical efficacy. This enantiomer is now marketed. All of the laboratory work was done at Columbia, including bioavailability studies and full kinetic profiles of the D and L enantiomers in animals and children. We are now looking at the development of new drugs used in children and psychopharmacology. But for many years, children were forbidden to be in studies of new drugs. So we have an enormous backlog of non-information, where drugs have been used in children, but we have no documentation, no evidence of the kinetics or even whether the drugs are useful. We have anecdotal evidence, but not hard data.

TB: Didn't you continue working with George Simpson after he left?

TC: He and I have worked closely since I first arrived in the US and for all of the years I have been here. He moved to USC, in 1978, but we still do collaborative work and are in contact roughly once a week. Jan Volavka came to the Nathan Kline Institute about two or three years later and took over the schizophrenia program, and he and I have worked together, closely, since then. I suggested to him that we look at controlling treatment by blood level, as for example, looking at haloperidol and controlling the treatment by blood level and not by the dose. We obtained years of grant support in that area. We were able to show that if you got patients into the 5 to 15 nanogram per ml range that was therapeutic, but if the level went higher you didn't achieve anything additional.

TB: When you say excessively high doses of haloperidol, what are you talking about?

TC: We had patients who were getting up to 70mg a day of Haldol, which by my standards is an enormous dose, and yet, when they were brought slowly down, most of them didn't deteriorate

and quite often got better. There was the occasional patient who showed massive deterioration on these very high doses. But there are other aspects to those patients, including that they could be rapid metabolizers with drug not reaching the central nervous system. As well as working with Jan Volavka, I worked with Don Klein at Columbia. We started lots of collaborative studies with Drs. Klein, Quitkin, Rifkin, Stewart, McGrath and Rabkin. I have also worked with John Mann at Cornell, Pittsburgh and now at Columbia on his suicide studies. This involves a lot of tissue work, levels of drug in the central nervous system and spinal fluid.

Of course, I don't just do drug metabolites. We've moved on into looking at neurotransmitters and their metabolites in the central nervous system. We have a large biochemical pharmacology laboratory, which covers a wide range of compounds of interest in biological psychiatry. We do a lot of steroid hormone studies: cortisol, prolactin, growth hormone, including the metabolites of these compounds. We have capabilities in gas chromatography, mass spectrometry, liquid chromatography, and various immunoassay procedures. This gives us powerful precise tools to look at what is going on with these compounds. We've moved from urine, which was the only thing we could measure, to blood, spinal fluid, tissue, and we are now measuring hair concentrations. It turns out that hair grows roughly one centimeter per month, and drug is deposited in the hair but doesn't get out because of certain pH conditions. So you can get a chronology of what's going on in a patient. We can section the hair into one or two month sections, depending on hair length.

TB: Isn't hair used for the detection of some drugs of abuse, for example PCP?

TC: Yes. One of the groups that work with me is Marc Larouelle's group engaged in PET imaging. Some of their studies involve patients who are abusing PCP or ketamine. If you look at the blood or the urine that gives you a picture of what has happened over the last couple of days. But if you look at the hair, you can get a picture of what has happened over the last six months, again depending on the hair length.

TB: Which are the drugs you have the methodology to study in the hair?

TC: We can do it in pretty much all psychotropics now. All of the second generation drugs we have routine methodology for and it's running continuously.

TB: All the different classes of psychotropics?

TC: Antidepressant, antipsychotic, and anxiolytic.

TB: What about the enhancers?

TC: We don't have much because I've not been asked to collaborate with people who are doing that. We do a lot of collaborative work with Dan Javitch, now at the Nathan Kline Institute. We are looking at the cycloserine, D-serine and lysine work, which he has developed. We've not done much in terms of the blood levels of the enhancers. But, technically, they're not that difficult. If we had projects, we would develop the methodology.

TB: Were you involved in research with monoamine oxidase inhibitors?

TC: We were involved with monoamine oxidase inhibitors with Donald Robinson and Alexander Nies. This was late 1970s and early 1980s. Robinson was at the University of Vermont, and heard we were measuring antidepressants. He had done this beautiful study with amitriptyline. Robinson came to me with the Rosetta stone; he had a completed tightly controlled fixed dose study with more than adequate plasma samples for each and every patient. We had just received the nitrogen detector, so we were able to do amitriptyline and nortriptyline and the hydroxyl metabolites easily. We had two or three hundred samples. We analyzed these and gave the results to Don Robinson. He came back with terrible findings. There was no correlation whatsoever between plasma level and a single outcome. We didn't believe this and tried to analyze it as many different ways as we possibly could, but it just didn't work out. After that, it turned out Robinson and Nies had done some of the pioneering work in monoamine oxidase inhibitors, and so we started looking at the methodology to measure these compounds. And they were not easy to measure. We focused on phenelzine, and eventually we were able to measure it using a mass spectroscopy method and deuterated standards. Then we tried to look at the monoamine oxidase level versus the inhibition, measured in the platelets. Robinson and Neis had shown that to get a full effect you had to have inhibition at 80% of the platelet monoamine oxidase. And that held up very well in clinical studies. We looked at the blood level of the monoamine oxidase, but one has to realize that monoamine oxidase binds irreversibly and so, once it's bound to the protein, it is actually degraded with the protein. It never comes off.

TB: Was any of the clinical work of that project done at the Nathan Kline Institute?

TC: No, they did that up in Vermont, and came to me to look at the metabolism of the compound. That's where my reputation was established, when people began to realize that collaborative studies were possible, and you didn't have to have a lab of your own. Don Klein and Ed Sachar at

Columbia realized that if they put resources in place at Nathan Kline Institute and my lab, this would work to the benefit of the Institute, the psychiatric researchers, and also to me. It was a very nice moment for me because that's the first time I had access to a mass spectrometer, purchased by Columbia.

TB: What was the technology you used before? Was it paper chromatography?

TC: Yes, you're right. The first grant I ever had was on iodinated amino acids, and I used paper chromatography. Now we're working with capillary columns which are 30 meters long which have separating powers I could never have dreamed of in the 1960s.

TB: Remind us what year did you get your first grant?

TC: In 1964.

TB: What about grants later?

TC: I've had grants in my own right. I got contract grants. I always have four or five collaborative grants where I am a co-investigator. TB: Did you have a grant together with Jan Volavka?

TC: Yes. Jan is psychiatrist and electrophysiologist and has been interested in the blood levels of drugs. He has also developed an interest in violence and aggression. I first met Jan when he was at Manhattan Psychiatric Center running the violence ward. That was my first real exposure to a ward with patients, chosen because of their violence. We collaborated with EEG work. He looked at drug levels, and we extrapolated to the brain. But the electrophysiology was 100% Jan and not me.

TB: What was the drug he monitored, haloperidol?

TC: Yes.

TB: Was there a linear relationship?

TC: That was specific for haloperidol, but we have done it for many other compounds. We try to keep ahead of the drugs that come onto the market. That was pretty easy in the 1980s because not too many drugs were introduced. It became a little more interesting with the advent of the SSRIs and the new generation antipsychotics. We are able to measure all of the antipsychotics and SSRIs on the market at the moment.

TB: Before they get to the market?

TC: Sometimes before, sometimes after. We do some work with drug companies where we look at Phase II studies and blood levels. With methylphenidate, we looked at the early Phase I trials

and early Phase II trials. We looked at initial kinetics in children. That was very interesting work, because it turns out that methylphenidate has two forms; the D form is active, the L is not.

TB: When did you do that research?

TC: This was done in 1994-1995. The drug came to market in 2002 and I understand, it is effective and doing well. What we found, which was very interesting, was when a patient is given a mixture, which is normal, the D level in blood is quite high, and the L level is virtually non-measurable. So there is extensive metabolism of the L form in the gut before it gets into the systemic circulation. That was a complete surprise. People were doing PET studies where D and L were given intravenously and were looking at the effects of both forms. We were able to show that the L form didn't really reach the blood. What they were looking at with L only, pertained to intravenous metabolism and not to gut metabolism. And no one gives methylphenidate by injection.

TB: Did FDA at a certain point in time become interested in bioavailability?

TC: We did a lot of work in the late 1970s and early 1980s on bioavailability of drugs for FDA studies. The FDA was put into a situation where there were many drugs on the market which have never been examined in terms of the kinetics and their bioavailability. The ACNP, about 15 years ago, had a whole symposium on the topic, because when a generic drug came onto the market, they were finding that it showed something called super availability. The new generic formulation was better than the old because more of the drug was available per unit dose. The conference was about how do you handle that but it was never resolved. When imipramine came to the market and was used extensively, there was no kinetic work because there were no available measures.

TB: Any other research in pharmacokinetics you would like to mention? Didn't you do some research with lithium?

TC: I've done a lot of work on the kinetics of drugs, and one of the things we found was we could predict dosage required to reach a certain blood level. We discovered this with lithium. We gave a single dose and 24 hours later we took a blood sample and showed the lithium level was highly correlated with what a patient would achieve on a fixed dose, and I emphasize a fixed dose. Once you had achieved that you could adjust the dosage to bring that patient into the range you wanted which at that time was between 0.8 and 1.2mEq/l. Since then, it has dropped considerably, but the methodology works. It has been used since 1972, when we first published this data and is still mentioned in the literature today. Some people say it doesn't work. Some people say it does.

Some clinical laboratories can't use this technology, because many of the instruments cannot measure lower lithium levels.

TB: When did you do that work?

TC: We did that, in 1971, and we published after we presented our findings at the ACNP. It was the first presentation I made at the ACNP.

TB: When was that?

TC: I gave my first paper here, in 1972, and then pretty much presented a paper every year at the ACNP. They are wonderful meetings where one can interact with people and scientists, both at the basic and the clinical level.

TB: What year did you become a member?

TC: I became a member in 1983.

TB: Are you still active in your research?

TC: Yes. I'm excited at the moment because PET is here. PET has been around for 15 years, but didn't really produce very much. There were nice pictures, but we didn't have the ligands or the technology that we have now. I would like to be able to continue to contribute in the area of plasma level monitoring, hair monitoring, and looking at spinal fluid, both drug metabolites and also neurotransmitters and steroids, in conjunction with PET studies. That is probably the most exciting area because we are looking at a living human brain. We can give it certain challenges and look at the consequences biochemically.

TB: I think we should conclude on that note this interview with Thomas Cooper. Thank you very much.

TC: Thank you.

15. DAVID L. DUNNER

TB: This will be an interview with Dr. David Dunner¹⁷ for the archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the College, in Hawaii. Could you tell us when and where you were born, something about your education and how you got into neuropsychopharmacology?

DD: I was born in Brooklyn, NY on May 27, 1940. My father was a general practitioner in Brooklyn, and just before the war, he decided to join the Veteran's Administration. He asked to go to the east coast, and not to a mental hospital. So, they sent him to the Menlo Park VA. At the Menlo Park VA, which is a mental hospital in California, he had quarters on the grounds. One of the patients asked, "Would you like some calla lilies in your garden?" He said sure. So, the patient transplanted the manager of the hospital's prize calla lilies to my dad's garden, and dad was promptly transferred to the Livermore VA. I grew up on the hospital grounds. Dad was active in TB research and involved in clinical trials with streptomycin. When I was ten, we moved to St. Louis for three or four years, and my father became head of regional TB studies for the VA. In 1954, we moved to Washington DC, when he became director of research for the entire VA. He lived in the Washington area until he died. So, I went to high school and college in the area. I went to George Washington University, and then to medical school at Washington University in St. Louis. I graduated from there and then took a one-year rotating internship at Philadelphia General Hospital.

TB: How did you get into psychiatry?

DD: When I went to medical school, I thought it might be nice if I was an internist and did research. I immediately took a disliking to both. Then, I thought maybe I should be a pediatrician. My first patient in pediatrics died. I decided that was not for me. I remember sitting in my dormitory room at the end of my third year at medical school flipping through a catalog of medical specialties wondering what would become of my life, and did I want to be an anesthesiologist? Then I came to psychiatry. At that time, the Department of Psychiatry of

¹⁷ David L. Dunner was born in Brooklyn, New York in 1940. He received his M.D. degree from Washington University in St. Louis. After his internship at Philadelphia General Hospital, he completed his psychiatry residency at Washington University. After a fellowship at the Intramural Program of the National Institute on Mental Health in Bethesda, MD, he was on faculty at Columbia University in New York and then at the University of Washington at Seattle. He was interviewed in Waikoloa, Hawaii on December 13, 2001.

Washington University was run by Eli Robins, and was very medical, non-Freudian. Psychiatry was the furthest thing from my mind when I went to medical school but these patients came in the hospital sick, got better with ECT, and were discharged within a few weeks. There was really an improvement, so I decided I could do that.

TB: Did Eli Robins have any impact on your decision?

DD: It was the whole department being non-Freudian and medical. Having decided to be a psychiatrist and to train at Washington University, I went out of town for a year to Philadelphia for an internship, and then came back to Washington University to do my three-year residency. Right around that time, men had a draft obligation in the military. You could defer it to become a specialist through the Public Health Service or the army. I applied for both and was accepted to both, and then decided to do the Public Health Service because my parents and my wife's parent both lived in Washington DC. So, it would be going home and spending time with our families.

TB: So you went back to Washington?

DD: Right. I finished my residency in 1969 and went from St. Louis to NIMH for two years. Because I was going to go to a place that specialized in research on manic depressive illness I talked to George Winokur, who was one of the teachers at Washington U. I said, "George, I need to know more about bipolar disorders, so I don't look like a fool when I go back east." So, I did a little research with him, which wasn't published, on the effect of ECT in the treatment of acute mania. Around that time, lithium was first being used. I remember we would have patients sign a consent form saying that they agreed to take the experimental drug, lithium carbonate, and the side effects included nausea, vomiting, diarrhea, tremor, and death. We went to the pharmacy, where they had these huge bottles of lithium carbonate, and asked them to make up capsules to give to patients. Lithium was exciting, and George Winokur, Paula Clayton and Ted Reich were doing studies on the genetics of bipolar disorder. So, I ended up at NIMH, worked with Biff Bunney and Fred Goodwin, and was paired with Elliot Gershon.

TR: As a resident, did you do any research?

DD: Not their research. I had summer jobs back in Washington DC in a laboratory.

TB: What did you do?

DD: The first job was at the Mt. Alto Veteran's Hospital, where I worked on tubeless gastric analysis with Dr. Sun. He published my first paper in a GI journal.

TB: What year?

DD: Probably around 1966, when I was a medical student. Then I did another summer research project with a person trying to look at antibodies that developed to TB and sarcoidosis. I was playing around in her lab staining pine pollen because there was a theory it had something to do with sarcoidosis. I found out that pine pollen was acid fast and we published a paper. That was number two. Number three came early in my days of NIMH. I happened to have lunch one day with Julie Axelrod. We got to talking, and he had a young person in his group, Cal Cohn, who had been working on an assay for catechol-O-methyltransferase (COMT). So we did a study looking at COMT in the blood of patients with depression, schizophrenia and controls. The results showed that the groups had different values. Julie, being a good scientist, did not believe it and asked us to replicate it. We got more blood, replicated it, and published the results in *Science*. It was the first publication that Julie had after his Nobel Prize. So from 1969 to 1971, I was at NIMH.

TB: So you participated in research on catechol-O- methyltransferase?

DD: Right. I did the assays if Cal Cohn was busy, but my primary job was to get blood from the patients.

TB: Did you find increased activity in any of the groups?

DD: No. There was decreased COMT in depressed women.

TB: What about in schizophrenic patients?

DD: Schizophrenic patients were no different from controls. My interest in bipolar disorder and clinical genetics stem from interactions with Elliot Gershon and having just come from Washington University where Winokur, Clayton, and Reich had published their book about the genetics of bipolar disorder. Elliot was somewhat skeptical about that but we had access to patients at NIMH. First, we reviewed all the charts of the patients who had been admitted over the previous 10 years and divided them into unipolar depression and bipolar disorder. In doing that, we found a group of patients who had depression and hypomania but weren't bipolar because they had not been hospitalized for it. They weren't unipolar so we put them in a separate category, and that is how bipolar II got delineated. It turned out that those patients had a very high suicide attempt and suicide rate. We identified that group, around 1969, and presented the data at a meeting in San

Francisco, in 1970. It took forever to get that paper published because I do not think people were quite ready for a subtype of bipolar disorder.

TB: Was that before or after Angst and Perris published?

DD: Angst and Perris had written their reports around 1966, but they had bipolar and unipolar patients. We were interested in replicating bipolar versus unipolar and found this bipolar II group.

TB: Could you tell us something about the place you worked at NIMH?

DD: It was a 15-bed locked research unit. There were inpatients with mania, acute mania or depression, who volunteered for research studies. There was a series of offices. Biff's and Fred's offices were on the left and I shared one with Elliot Gershon on the right. There were some secretarial offices. When we were second year clinical associates and Bob Post came in as a first year clinical associate, we moved across the hall and had a window office. Further into the unit, there was a day room, a nursing station, and down the hall there were patient rooms. What we were studying was the chemistry of bipolar disorders and treating patients with L-DOPA and α methylparatyrosine. We were studying cerebrospinal fluid (CSF) and using probenecid to block the outflow of 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA), then measuring their accumulation in CSF to see if we could show chemical effects of drugs or differences in patients. We were also looking for COMT and dopamine β -hydroxylase enzymes in blood as they were being discovered. We were collecting urine and looking at MHPG, a forgotten substance these days. The patients were all volunteers and stayed on the inpatient unit at NIMH for sometimes about a year. After being part of a study, they would be treated and discharged back to their community.

TB: By the time you did this research, you had discovered bipolar II?

DD: By that time I had discovered bipolar II.

TB: What else did you work on at NIMH?

DD: I was working on some early genetic studies with Elliot Gershon. Around the end of our first year at NIMH, Gershon and I proposed a family study of bipolar and unipolar depressed patients, interviewing relatives, and drawing blood for enzymes of interest. We invited the regular faculty of NIMH like Bunney, Goodwin and Axelrod to join us in this project, but they thought we were kind of crazy. No one believed that these were genetic disorders at the time, and the notion that you would interview relatives did not appeal to anyone as having scientific merit. To get ahead a

little bit, Elliot went on to Israel and I went on to work in New York with Ron Fieve to do those studies. These early studies on the genetics of bipolar disorder did not arouse great scientific enthusiasm because everybody thought the illnesses were mainly psychosocial.

TB: So you were back to bipolar illness that you first became interested in at St. Louis?

DD: It started in St. Louis because I knew I was headed to NIMH. If I had been heading to NIMH to work on schizophrenia, I probably would have wanted to be more involved in schizophrenia in St. Louis. Washington University was one of the few places in the country at that time that diagnosed bipolar disorder. So, I learned the Washington University diagnostic system, which was the forerunner of DSM-III, when I was a first and second year resident.

TB: Could you say something more about the program at Washington University?

DD: It has always been called a biologically oriented program. The preferred word was medical. It wasn't that they didn't believe in psychotherapy, they didn't believe in anything. They had what was called an agnostic approach which was data driven. So, if you had data to support a position, then you had some way of conversing with other people. Otherwise, it was all supposition. The diagnostic system in use at the time was DSM-II, which had paragraphs of descriptions with no exclusion criteria. That diagnostic system was, by and large, ignored by the faculty at Washington University, who instead relied on their book of research papers. These involved descriptive, follow-up and family studies. Eli Robins and Sam Guze had written a paper around 1960 or maybe 1970, on how you differentiate one schizophrenic syndrome from another. Eli Robins used to have a meeting once a week with all the residents. We would present a case, and he'd expound upon whatever he wanted to expound upon for as long as he wanted to expound upon it. He was the professor, so we just sat there. He was encyclopedic in terms of his knowledge, and a wonderful man. At that time, he was still walking. The disease that ultimately took his life had just begun, but he was still very mobile. His wife, Lee Robins, is one of the premier epidemiologists in the world. There were several other important people in the department. George Winokur was in charge of the first year residents and we presented cases to him regularly. Sam Guze was very active in the outpatient department and consult service and we saw him more as a second or third year resident. Paula Clayton was an assistant professor at the time. She just had a couple of children and was mostly teaching in the outpatient department. Ted Reich was a resident who was a year ahead of me. Bob Cloninger was a resident a year behind me. John Feighner was in my residency class. John went on to do wonderful things in psychopharmacology. Dennis Cantwell,

who died a few years ago, the famous child psychiatrist, was in both my medical and residency class. We had a very large group of co-residents. Other people who were there include George Murphy, who was the primary person who taught us psychotherapy. He went on to do some cognitive behavioral psychotherapy studies at Washington University. A fellow named Bob Woodruff joined the faculty from Harvard around the time I was a second year resident, and unfortunately, died six or seven years later. He was a wonderfully warm, bright person who was another kind of no nonsense Washington University person. If he didn't have data, he just could not talk about a problem realistically.

TB: He wrote the book on *Psychiatric Diagnosis*?

DD: Right! And he was really loved by all of the trainees. The interesting thing about Washington University is that it was so different from American psychiatry, which was dominated by psychoanalysts. We thought we knew the right stuff. Everybody else thought they knew the right stuff, so we would go to meetings and nobody talked the same language. We were data driven and descriptive, while other psychiatrists were analytic and impressionistic. We were using treatments, including medicine and ECT, and were well trained in how to use the medications of that time. That was minimized in most American training programs in favor of analytic therapy. We used different, non-analytic, therapies. I remember treating a patient who had fetishes using skin shock behavior therapy. We used other forms of behavior therapy that were just coming out. We were also taught by people who were Freudian. Ed Gildea, the chairman before Eli, had a wife who was a Jungian analyst and she taught us. The difference in Washington University from other places was there wasn't a dominant therapy that everybody adhered to. When we didn't know, we had to find out and that meant research. So, all of the faculty were active in research.

TB: Tell us something about the research done by the faculty.

DD: Lee Robins, and her work in sociopathy, is a good case in point. She studied conduct disordered children to determine which behaviors were associated with the disorder and with adult sociopathic behavior. "Deviant children grown up," was a description of adult sociopathy. We used our own diagnostic system with disorders like primary affective disorders. Schizophrenia was a chronic disorder. We had mania; it wasn't even called bipolar then, and alcoholism. There wasn't that much street substance abuse at that time; it was mostly alcoholism and barbiturates. Rarely would we see anybody with heroin abuse. Sociopathy and Briquet's syndrome, hysteria,

were both identified through follow-up studies. The goal was to have a descriptive psychiatry, so that if you saw a patient and they met criteria for a diagnosis, you could predict the treatment and outcome based on follow up data. That also left a group of patients who did not fit into the system very well; so about 20%, were called undiagnosed. We had 10-12 major diagnoses summarized in a paper authored by John Feighner, in 1972, called, "Diagnostic Criteria for Use in Psychiatric Research." These were the clinical criteria we were using as residents. Follow up studies on the undiagnosed patients found that they stayed undiagnosed over time. So, there was stability in that category also. You didn't have to diagnose everybody.

TB: Didn't they use external validators?

DD: There wasn't any good way to externally validate anything. I am not sure there are good ways to externally validate diagnosis, but if you have a laboratory test that can help. But descriptive, follow up and family studies were what really drove Washington University and the different disciplines that contributed to structured interviews. As a resident, I was doing the Renard structured interview, which was a collection of instruments that later became the Schedule for Affective Disorders and Schizophrenia (SADS). The Research Diagnostic Criteria were the forerunners of DSM III. Washington University went on to develop its own Diagnostic Interview Schedule (DIS), but we were doing this kind of stuff as residents. We would ask patients to go through checklists of symptoms because that helped us with diagnosis and prediction of outcome. Then, we could tell the family if a disorder might become recurrent or chronic. It was a very exciting time, and I think Washington University and lithium have contributed greatly to contemporary psychiatry in the United States. Washington University, because it recognized mania and developed ways to diagnose people with bipolar disorder, became important for American psychiatrists to diagnose and treat bipolar disorder with lithium. The evolution of DSM-III from DSM-II was a major contribution by Washington University pioneers like Eli Robins, Sam Guze, and Bob Woodward. They, in turn, influenced others like Bob Spitzer and Gerry Klerman, leading to the development and use of structured instruments such as the SADS and RDC in clinical practice and research. We still had some differences of opinion. The DSM criteria for diagnosing schizophrenia required only two weeks of illness, but at Washington University, it was six months because our follow up data showed that duration predicted outcome. The lengthy illnesses we called schizophrenia usually didn't recover. Others call the Washington University

approach “biologic,” but I would call it descriptive. It was data driven, and if the data changed, we would modify the criteria. An example is Briquet’s syndrome, which is now somatization disorder. It went from a checklist of about 60 symptoms, divided into 10 different categories, to the current DSM-IV system, which is probably 30 symptoms in five or six categories. My understanding is you can get the same degree of reliability in diagnosis with about 10 symptoms, if you are positive about a certain sub group.

Washington University was never very good about treatment studies. It wasn’t their thing. We used amitriptyline, lithium, ECT, and chlorpromazine but weren’t doing treatment outcome research or clinical trials. It was descriptive, and later became more image-driven using techniques developed by Mallinckrodt. When I was there, psychiatry had the third largest biochemistry laboratory department in the medical center, and the most labs after pharmacology and biochemistry. Psychiatry was very active in basic research, including Eli Robins’ work with brain proteins. He was an excellent clinician, who also had a research laboratory. Not everybody on the faculty worked in a wet lab, but everybody did some kind of research. All the residents had to have a three or six month research component to their training, and most published papers. I did not. I worked with Lucy King in her lab and did research on rat brain epinephrine and norepinephrine in sleep deprived rats. We didn’t find anything worth publishing. That was one of the few research areas that I never published in.

TB: What was your background in research before you joined NIMH?

DD: My first exposure came through my father, who was active in research. Then, at Washington University, psychiatric research was just what we did. If you wanted to find an answer, you did research. Inquiry was important. After that, the focus on mood disorders came with the choice I made of going to NIMH with the Public Health Service and being accepted into a group that was studying the chemistry of manic depressive illness. I think the reason I was selected at NIMH was my background in diagnosis at Washington University. At the end of my first year of a two year commitment, it looked as if I might go into private practice. Keith Brodie was chatting with me before he left to go to Stanford, after finishing his two years at NIMH. He suggested I consider working with Ron Fieve in New York and continue my studies on bipolar disorder. I didn’t want to live in New York, but Peggy and I visited and got offered a job. We ended up finding a house in New Jersey, within easy commuting distance. I spent the next eight years at New York State

Psychiatric Institute, working with Ron Fieve at Columbia University, in the Lithium Clinic. He had several hundred patients that he was treating with lithium and antidepressants. He also had an inpatient research unit, which I was in charge of and we continued to do spinal fluid and treatment studies, including the use of L-DOPA and Ltryptophan. Ron was working on rubidium, another metal in the lithium chain that seemed to help depression. Unlike the NIMH, we had a very large outpatient clinic where we did studies. Using the Washington University approach to diagnosis, I wanted to see if clinical, family, or biological factors could distinguish primary affective disorders from bipolar disorders and depression from manic depression, looking at bipolar II as a subtype. We published a large family study at that time. It was an exciting time for me, scientifically, because Ron was very helpful in introducing me to people like you. I went to my first ACNP meeting in 1972 and joined the college around 1974. I don't remember the exact date, but at that time, meetings were mostly in Puerto Rico, though occasionally California. I met people like Max Hamilton. Our group at Columbia was right next door to Joe Zubin, a wonderful person who had tremendous influence on American psychiatry. He was a psychologist, who helped developed the DSM-III system, and Bob Spitzer had worked in his lab. Joe was very sympathetic toward research and less so to analytic psychiatry. We were doing research that made sense to him, so we became friendly. I remember having lunch with Joe and Max Hamilton, and meeting this grumpy, old English man, who never seemed to have a nice thing to say, but with a little twinkle to his sneer. It was exciting for me as a very young person. ACNP, at that time, had maybe 200 members. It was easy to have lunch with a basic scientist or another clinician, and much less complicated than it is now, where you have to hunt for people or make appointments to see them. There were fewer sessions, and a coffee break that everybody went to, so one could easily find people to chat with.

TB: Were the meetings still at the Sheraton?

DD: At the Caribe Hilton more than the Sheraton. While at Columbia, I wrote about 50 papers and started to do national talks. I always tried to present at Biological Psychiatry, the APA, and ACNP. Those were meetings I targeted, and I tried to write a paper for each occasion. One year, when I wanted to get promoted to associate professor, I wrote something like 14 papers. Both my wife and I felt that New York was not a forever place for us, and I started

looking around. It's easy to leave angry, but hard to leave friendly. It was important to me that I leave Ron in a friendly way, which I did. We are still close and do collaborative work because he was very important in developing my career.

TB: Could you tell us something about depression research at Columbia?

DD: We were interested in differentiating depressive subtypes, looking at bipolar I, bipolar II and unipolar diagnoses from family data and symptom differences in clinical studies, including psychological and personality tests. We did treatment outcome studies, and it was through those that we developed the concept of rapid cycling. In the early 1970s, lithium was used a lot. It had gotten positive reviews in Europe but had been very negatively viewed in the United States, where it had actually been taken off the market because it had been used as a sodium substitute in cardiac patients and deaths occurred.

TB: That happened long before.

DD: That was before. But in the early 1970s, there was this turmoil about whether to treat mental disorders with medications or psychotherapy, and most departments were dominated by people who were psychoanalytically oriented. There were a number of early drug trials in depression using tricyclic compounds like imipramine or amitriptyline. Haloperidol was starting to be used, right around the early 1970s, for acute mania, but while there was some interest in what became psychopharmacology, it wasn't a big part of many training programs. Ron Fieve's major effort was to get wider acceptance of lithium. When patients from our lithium clinic went on vacation, it was difficult to find physicians they could consult who knew about the drug. The positive side of lithium was a driving force for Ron, while I looked at those who didn't respond well. He called me the negative guy in the department. To decide what it was about people who didn't respond to lithium we started looking at their age, age of onset, gender, family history and prior episodes. We rated episodes in the two years prior to lithium treatment and found that had great predictive value. People who had four or more episodes, in the two years prior to lithium treatment, were most of the lithium failures; people who had fewer episodes generally did better.

We published that paper, and that is how rapid cycling got started. It turned out we weren't the first to identify that group. There was a Canadian psychiatrist and others before. Bunney's group at the NIMH was studying 24 hour cyclers. Anyway, we got the credit with our paper. It

was published around 1974 and titled, “Clinical Factors in Lithium Carbonate Prophylaxis Failure.” Ron and I were the authors.

TB: Who was the Canadian psychiatrist?

DD: I will get his name later.

TB: Was he Paul Grof?

DD: No, it wasn't Paul. At that time, I was going to more meetings and talking about bipolar and unipolar distinctions in lithium treatment. Sid Malitz and Sandy Glassman's group at Columbia, down the hall from us, were treating mostly unipolar depression. We had a large clinic with a lot of students. We helped train people like John Nurnberger, Norman Rosenthal, and Mike Liebowitz who wrote their first papers with us. Steve Roose worked with us early in his career. Part of their training at Columbia would sometimes involve research and time with our group. I always made sure they got a paper out of it because almost anything you studied revealed something new that could be published. I once had two papers in the same Archives issue. We were writing and publishing a lot, it was exciting, and I felt good about mentoring people. I became involved more with teaching, lecturing, and continuing medical education (CME) presentations. Prior to the mid 1970s, I didn't travel very much, but all of a sudden, I began to get invited. It was very exciting. But it came time to leave. Mark Schuckit, who was a resident at Washington University, a couple of years behind me, suggested I look at the University of Washington, in Seattle. Carl Eisdorfer was chair and they were recruiting to replace their psychopharmacologist, Bob Friedel, who had just left. I never thought of myself as a psychopharmacologist, but more as a descriptive psychiatrist, who does clinical trials to study patients and their outcomes. Anyway, I looked at the job but it wasn't quite right. Seattle seemed OK, Mark was there, and it was a nice department. I liked the people. They had another opening as chief of psychiatry at Harborview Medical Center and asked me to look at that. My wife Peggy liked Seattle and I saw things in the job that were very positive. It would enable me to continue research in bipolar disorder, and I could set up the kinds of things that I had been doing with Ron in family studies but broaden it to do more teaching. Also, there was some interest in anxiety disorders. Pete Pitts, who was at Washington University when I was, had done lactate infusions in panic but, when Pete's son developed leukemia, he dropped out of research. That idea got buried for a while, but Don Klein picked it up and was starting to do lactate-infusions at Columbia. I was really very interested in looking at children

who might become ill. Again, assuming that panic was a genetic disorder in which children would develop the illness later, maybe we could develop family studies in anxiety disorders. When I took the job at the University of Washington, became professor in the department and head of psychiatry at Harborview, there was a small clinical trials program that Eisdorfer was running. His area was ageing, but he had contracted to do a study in anxiety. He was going on sabbatical and asked if I would take over those clinical trials. At that point, he had one or two ongoing trials, a part time research coordinator and a doctor looked in on the patients. While he was gone, we developed an immense clinical trial program at Harborview. Within five or six years, we had 26 ongoing studies in areas like schizophrenia, depression, panic disorder, generalized anxiety disorder, smoking, dementia, and sleep. We developed a huge staff, using the money to fund younger researchers at the University of Washington.

TB: In what year?

DD: I moved there, in 1979, and was chief of psychiatry at Harborview for a little over 10 years. Those who were involved with me were people like David Avery, who was hired to do ECT and research studies, Steven Dager, who has become an excellent neuro-imager, Debra Cowley, who is our training director at the University of Washington; Deb and Steve were residents together and collaborated in studies on panic. We did get a couple of grants to look at high risk children with depression and panic, working with child psychiatrists, Bob Reichler and one of his colleagues, Carrie Sylvester, who is now at the University of Illinois. We put together a program, funded primarily from psychopharmacologically driven trials through industry, and used them to get patients to do family studies similar to what I had been doing in New York, except that the populations were obtained from clinical trials. The high risk studies never panned out, but people from the group went into neuroimaging, like Steve, or back to depression and bipolar studies, which I focused on in the mid 1980s. I set up The Center for Anxiety and Depression because we had a lot of faculty expertise in Seattle, and developed a consulting service for local clinicians, and also a way to do research using structured assessments of patients. That era really led into more clinical trials and a big bridge with the community in terms of being the primary person in Seattle for consultation on treatment resistant patients. Now, I am the clinical expert in bipolar disorder and treatment resistant depression in the Seattle area, involved in clinical trials mostly in mood disorders but still wanting to do family studies. We are trying very hard to get funded for a family

study dividing unipolar depression into subtypes. We continue some interests in bipolar disorder, but I like to go where people haven't been because it is more fun.

TB: Didn't you collaborate with John Feighner on fluoxetine?

DD: John Feighner was a residency classmate of mine. He developed this excellent clinical trial group in San Diego, and drug companies were interested in having him study new drugs.

One of them was fluoxetine, and he had contact with Paul Stark, who was a PhD and worked for Lilly. We studied fluoxetine, until it was approved by the FDA. We had, I think, a quarter of the Prozac patients involved in Lilly's clinical trials, not all of them positive. Our primary work was with Upjohn on alprazolam (Xanax) in panic, because they were funding our lactate infusions and studies of mitral valve prolapse. So, patients who were undergoing studies with Xanax, were actually part of the research on lactate infusions and echo cardiograms for mitral valve prolapse. If the subjects had children, we put them into our family study. Upjohn was funding us to a much greater extent than Lilly, although we went on to do a whole bunch of studies with other companies. We were involved in clinical studies of every single drug on the US market, at least once, if not many times.

TB: All kinds of psychotropics?

DD: Antidepressants, anxiolytics, and early on, in studies of an approach for dementia. When I was at Harborview, because we had an inpatient service, we looked at some new neuroleptics, some of which have never come to the market, and some like risperidone, did. We also got involved in doing some psychotherapy studies. That came a bit later. I took over the outpatient department at the University of Washington, around 1990, where residents learn how to treat outpatients and do psychotherapy. In most psychiatry outpatient clinics, residents learn psychotherapy from the head of the clinic, who is a psychotherapist. I wasn't doing any psychotherapy and hadn't seen a patient in psychotherapy since 1976. But now, people were getting certified to be therapists using techniques like CBT and IPT. I thought if we weren't going to teach them to do what I did, we would at least teach them to do something that was data based. We began to certify faculty in CBT and IPT, so we could teach manualized psychotherapies to our residents. That is still going on at the University of Washington. We took things like the Barlow Manual for panic because we could expose residents to data that supported the treatment. This isn't very different from my earlier training at Washington University. If you have data to say

something works, you go with the data. Around that time, we developed studies in CBT and dysthymia. Nobody was studying dysthymia much, so we got interested in that. I did a fluoxetine and CBT comparative trial in dysthymia. Earlier I was a coprincipal investigator with Joe Becker on an application for the collaborative treatment of depression, which the University of Washington didn't get. I am going to talk a little bit about psychotherapy. Not that I am a psychotherapist, but I like research. For years, there was a famous psychologist at the University of Washington, Neal Jacobson, and we had been having meetings every year about doing some collaborative studies. Finally, about five or six years ago, Neal wanted to do a study comparing his psychotherapy, behavioral activation, to CBT. We collaborated on that project, which was federally funded. It was a four cell design where depressed patients got behavioral activation, CBT, paroxetine, or placebo. I was in charge of the psychopharmacologic part. Unfortunately, Neal had a heart attack and tragically died two years into the grant. I then became the principal investigator, which I am today. Through that I became involved with other psychotherapy studies. Marty Keller was doing a large trial in chronically depressed patients that was funded by Bristol Myers Squibb, looking at metazodone and a new cognitive behavioral analysis system of psychotherapy (CBASP). We became one of the study sites and trained psychologists in our outpatient clinic to be certified in CBASP. I like that therapy, it is interesting. There is no perfect or single way to help patients and if combined treatment works, so much the better. By the way, the name of the Canadian scientist who first identified rapid cycling is Harvey Stancer.

TB: Harvey Stancer from Toronto?

DD: Yes, he published a paper about a year before ours, which described lithium failure correlated with more episodes. But he never got the credit for it. I am not directing the outpatient clinic anymore, instead I direct the Center for Anxiety and Depression, doing clinical trials and descriptive studies. At present, we are trying to get funding for a very large family study of unipolar depression.

TB: You mentioned the study you collaborated on with Keller.

DD: The studies that we did on dysthymia and the Keller study led us to work extensively on people with chronic depression. When you deal with treatment resistant depression, all of the patients are chronic with illnesses lasting two years or more. Psychiatry these days is really dealing with treatment resistant chronic depression. So, it is important we learn more about it, but,

having said that, I came to the belief that DSM-IV splits categories too much. It makes more sense to combine the different forms of chronic depression into one category. Right now, we have chronic major depression, dysthymic disorder, dysthymic disorder complicated by major depression, and a chronic form of depression that begins with a major depressive episode, but people don't get better even if they lose the criteria for major depression. That is called major depression in incomplete remission. To me all of these are similar. The four entities are not that different, and in many ways, they are confusing for clinicians. It is simpler to simply see a patient who has been sick for a long time. Unipolar depressions could be separated into acute and chronic forms. We are doing studies that we hope have some interest for people working on DSM-V to differentiate these subtypes and their course of the illness. This is the kind of work that I enjoy and like to do, using a very structured history on the large number of patients I see in clinical trials.

TB: What would you say was your single most important contribution?

DD: Training people who have gone on to do great things. I mentioned a few of them, and I am very proud of my association with them.

TB: What about research contributions?

DD: The bipolar II and rapid cycling concepts are probably the things most identified with me. Those are descriptive concepts. They are not biologically or family based but they describe groups of patients and their longitudinal outcome. I am disappointed that we have never identified the "bipolar gene." I started off with Elliot Gershon 30 years ago to find the gene for manic depressive illness, which we hoped to discover that summer. I realize now how complicated it is and how naïve we were. Very good people are now looking for the genes, not a single gene. I am not going to be the one to find them, but it would be nice to know that there really are genes when patients ask, "Is this a genetic disorder?" and I can only say, "Well, we think so." At Washington University, if we don't know, we are not going to make it up. People ask me how drugs work and I tell them I don't know. I can tell them what we think but in real life we really don't know. That is OK with me because our treatment outcome studies prove they do work.

TB: Could you mention some of your important papers?

DD: I mentioned the rapid cycling paper and the paper on bipolar II. It was written with Elliot Gershon and Fred Goodwin and took forever to get published. We presented that data in 1970, at APA, and it was turned down by a couple of journals for reasons nobody really understood. People

did not recognize bipolar and unipolar, let alone bipolar subtypes. It was a very good paper and was finally published in *Biological Psychiatry*, in 1976. We also did a longitudinal study of lithium and placebo treatment in bipolar II, and found effects for mania, but not depression. Don Klein came to the Psychiatric Institute shortly after that, and we gave him our computer program for analyzing data. The computer was almost as big as this room. It was a complicated analysis, but Don found something wrong with the program and asked us to retract the paper, which we did. But in the course of reanalyzing the data over two and a half years, rather than one year, we showed that lithium also had maintenance effects against depression in bipolar II patients. That information was buried in a letter to the Archives, when we corrected the first paper but expanded it. So nobody knows about it but it was an important contribution. The other thing that I have enjoyed doing has been to be at the crest of the wave in psychopharmacology. I alluded to that this morning. I was always in the right place at the right time. I was at Washington University when we worked on diagnosing mania but nobody else knew how to do it. I was at NIMH when we developed the concepts of bipolar II and did family and linkage studies that others only started doing later. We also did biological studies in mania and depression when there weren't a lot of things like that going on in the country. I was in New York with Ron Fieve when lithium appeared in what has been called the psychopharmacologic revolution, and I was right in the middle of it. I was knowledgeable about drugs and began to do clinical trials to study new drugs and psychotherapies. I was on the front lines and it was exciting. Later, my career shifted to more administrative activities, which was okay because I still was able to do research, which I find fun. I still like to come to the ACNP. I always have a poster or a paper, and I presented a poster at this meeting. I like to do that.

TB: What was your last paper on?

DD: I have one coming out next month on citalopram treatment of dysthymic disorder. This past year, we had one on sub-typing chronic depressions and I have written a couple of review articles on chronic depression.

TB: So your current work is focused on chronic depression?

DD: Right now it is, though, I still have a good deal of interest in bipolar disorders and mania. In the 1970s, everybody was interested in studying mania, but around 1980, people became interested in studying depression and anxiety, and very few people were doing anything in mania. It has

only been in the last couple of years, especially with valproic acid, that people became interested in studying mania again. We have still been doing descriptive studies in rapid cycling and in bipolar disorder. I have two things I am working on now. One is a study of who becomes hypomanic in response to antidepressant treatment, and the other is about defining the term chronic. Is it two years of illness or, in our data, it appears one year might suffice? Both of these studies have some implications for DSM-V.

TB: Did you publish any books?

DD: I edited a textbook, *Current Psychiatric Therapy*, which went through its second revision. That was a lot of fun. When I was President of the American Psychopathological Association (APPA), I designed the meeting and edited a book that was titled *Relatives at Risk for Mental Disorders*. The meeting focused on high risk. For six or seven years, I have been co-editor with Jerry Rosenbaum on an annual volume called the *Psychiatric Clinics of North America Annual of Drug Therapy*. I am the editor of *Comprehensive Psychiatry*, a journal that actually fits my interests because it is a journal of descriptive psychopathology, which is what I am and what I do. I am also on the editorial board of about 10 journals.

TB: Have you received awards and honors?

DD: I got the Samuel Hamilton Award and the Morton Prince Award from the APPA. I received the Robert Jones Lectureship from the Canadian Psychiatric Association. This spring, I am going to be receiving the Ward Smith Award at the annual meeting of the West Coast College of Biological Psychiatry, a 25-year-old organization of west coast mental health researchers that Biff Bunney founded. I have been president of that. I have been president of the American Psychopathological Association, president of the Psychiatric Research Society, president of the Society of Biological Psychiatry, and a fellow of ACNP.

TB: Let me ask you about your activities in ACNP?

DD: ACNP has always had the problem that we don't know how to appoint new members. When I was elected, they created a category of scientific associate which I became. A few years later, they decided that didn't make any sense because some really prominent people were scientific associates, and so it made all the scientific associates members. I have been on a bunch of committees, and I like to do that when I am part of an organization. So, I set up a symposium, I was on committees, but in order to be a committee chair, you had to be a fellow. In the early 1980s,

I was appointed chair of the education training committee. I was really excited by that because I knew it meant I had been elected to fellowship. I have only missed one meeting, since 1972, and I think I presented at each meeting I attended. For the last several years, I have usually nominated someone for membership, and I have been on a number of committees and task forces for ACNP. I love coming here. The organization is a lot bigger than the original 200 people, but you learn an awful lot coming, sitting, and talking with people.

TB: Is there anything else that you would like to add?

DD: I think family is something that never gets covered. My wife didn't come with me during the early times when we were in New York because we had young kids at home and it was right before Christmas. But since we moved to Seattle, Peggy has come to just about all the meetings and that has been a very integral part of enjoying them. You structure your life around meetings and this one is on my calendar for the next couple of years.

TB: Well, thank you very much.

DD: Thank you very much.

16. BURR S. EICHELMAN

TB: This will be an interview with Dr. Burr Eichelman¹⁸ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Tell me about yourself, where and when you were born, and something about your education?

BE: I was an only child, born in one of the Chicago suburbs, Hinsdale, and grew up in Downers Grove, another suburb. My parents wanted me to be a physician and started me on piano, so I could be a good surgeon. I appreciate that, although I didn't become a surgeon. Their expectations fortunately meshed with my interests in biology and in medicine, and I proceeded in that direction. In terms of college studies, I went to the University of Chicago, and looking back, appreciated a general education, so that even though I had an interest in biology and in science, I was forced to read the classics in the process of my college education. While at the university, I became interested and fascinated in the synthesis of morality with biology and behavior, as I saw others involved with these mind-brain kinds of issues. Such research was becoming very exciting, particularly in the areas of limbic function. For example, one could control sleep or appetite or sexual behavior by stimulating or lesioning parts of the brain.

TB: Did you do any research as a student?

BE: In that context, I began to work with Dr. Robert McCleary, who was an MD, PhD trained at Hopkins. He was a professor with appointment in biopsychology at the University of Chicago. I enjoyed his college course and was accepted at the medical school in an advanced placement, after completing my bachelor's degree in biopsychology in three years. In the summer hiatus between college and medical school, I worked in his laboratory. There, I believe serendipity played its first role in my career.

At that time there were some papers published out of Illinois Wesleyan College on pain-induced fighting in animals. If one provided a painful stimulus to rats, snakes, or monkeys, the animals would attack each other. Dr. McCleary suggested I find out about this and explore it in

¹⁸ Burr S. Eichelman was born in Hinsdale, Illinois in 1943. He received his M.D., Ph.D. from the University of Chicago. After an internship at the University of California, San Francisco, he moved to the Intramural Research Program of the National Institute on Mental Health, in Bethesda MD. He did his psychiatry residency at Stanford University. His first faculty appointment was at the University of Wisconsin in Madison, Wisconsin, an institution to which he ultimately returned after positions at the University of North Carolina at Chapel Hill and at Temple University in Philadelphia, Pennsylvania. He was interviewed in San Juan, Puerto Rico on December 9, 2003.

the laboratory. I went there and learned the procedure and, on my return, I did limbic, amygdala lesions in the rat and reconfirmed in this model what had already been noted in other studies that amygdala lesions modulated aggressive behavior.

This research and preliminary findings “stayed on the shelf” while I went to medical school, where I was accepted into probably one of the first public health supported MD/PhD training programs. So the federal government and the university played a very big role by supporting a married medical student, and by assisting with tuition and a living stipend. The University of Chicago also allowed an overlap in my medical school and graduate school courses, so that many of my PhD. courses could also count for medical school and vice versa. I completed my preliminary examination during the four years of medical school, actually during my third year pediatric clerkship, and then spent an additional year working up this model of pain-induced aggression in the rat in the context of limbic lesions. This led to my first publication in the *Journal of Comparative and Physiological Psychology* as a lead article. During that time, Danny Freedman had come to Chicago as Chairman of Psychiatry and it was clear that biology was going to play a major role in psychiatry. Though the neurosurgeons had coaxed me into a senior elective sub-internship, Freedman’s very compelling personality and mentorship really won out and directed much of my post-MD training.

TB: What year was this?

BE: I completed my M.D. degree, in 1968. Danny must have come to the university, in 1964 or 1965. I met with him to ask for advice about “what to do next.” He advised me to do a pediatric internship to see normal development at the same time as I was learning additional medicine. As a consequence, I matched at the University of California, San Francisco, in pediatrics. In that same intern class was Phil Berger, who has been another member of the College. He was a co-intern with me. Three of our eight interns subsequently went into psychiatry.

On the day I passed my oral PhD exams in Chicago, the movers arrived to relocate my wife, son, daughter, and myself to San Francisco. I stayed for that academic year in San Francisco, learning general pediatrics. During that year, I had applied for a post-doctoral fellowship at the NIMH, which was at the time a lock-step career development pathway for young clinician researchers interested in an academic career. I had been accepted into Dr. Fred Snyder’s Laboratory of Clinical Psychobiology. This was a sleep research laboratory that Herb Meltzer,

president of our college, as well as Chris Gillam, a past editor of our journal, and Dave Kupfer, another ACNP past president, had worked in.

TB: What areas of research did you work on at the NIMH?

BE: During my internship, Fred had called and asked what I wanted to work on. I replied that I would like to resume the rat work that I had been doing on aggression. I had shifted to the study of injecting neurotransmitters into brain regions which Pete Grossman at Chicago and Sarah Leibowitz at Rockefeller had been doing with feeding behavior. Fred agreed that I could continue this research at the NIMH.

I arrived in the summer of 1970 at Fred Snyder's laboratory. Shortly after, Irv Kopin's group spoke to Fred about some aggressive rats in their lab and how to evaluate them. These were rats that had been fed a carnitine-free diet. So Fred suggested I look at the rats. They were perfectly docile. In fact, in all the time that Irv continued with this research, he never saw the aggressive behavior again. However, in the cages above these carnitine-deficient rats, were some rats that had been treated by Larry Ng, with 6-hydroxydopamine. These were huge 750 gram rats, sitting up in their cages. I suggested to Larry that we just test them in my paradigm for shock-induced fighting. He agreed, so we wheeled them up to my lab.

These animals were about three to four times as aggressive as control animals even though they didn't look like it, when handled. This started my behavioral neurochemistry collaboration with Irv's laboratory. At that time Nguyen Thoa, a Vietnamese pharmacologist was there with Larry Ng, a neurologist, and Friedhelm Lamprecht, a German post doc. Redford Williams, also a fellow of the college, was there as an internist. It seemed at that time that everything we touched was statistically significant.

TB: Can you tell us about your findings?

BE: We published work with catecholamine depletion using neurotoxins. I did some work with Redford showing that sympathetic activity differed if the animals received stress when they were shocked, versus when they had the opportunity to attack another animal, suggesting that the attack paradigm was less stressful. We did some work with Friedhelm showing that animals stressed and immobilized for a month and allowed to recover so that their blood pressure reverted to normal, and they looked normal to handlers, remained two to three times as aggressive as non-stressed controls. Moreover, they had durable changes in brain enzymes such as dopamine- β -hydroxylase.

We did some genetic work and showed that various strains of rats had significantly different levels of aggressive behavior. This returned me to the question of how do brain chemistry, genetics, and environmental stress lead to issues of human aggression, law, and morality. With this work, my two years at the NIMH ended.

TB: What did you do next?

BE: I guess I could have stayed for an intramural career, but I have always straddled the clinical and basic science spheres, so I accepted a residency in psychiatry back at Stanford during the tenure of David Hamburg, who had been working with stress and aggression. It seemed like a natural environment for me. I had negotiated with Stanford to do two years of clinical psychiatry and a third year of residency in the laboratory, working with Jack Barchas, also a fellow of the ACNP.

Shortly after my arrival, I was informed that the department had lost their training grants and I would need to be doing clinical work during my third year, not full-time research. Jack was nevertheless very gracious with his laboratory support. At that time, Roland Ciaranello and Donna Wong, also past and present members of the ACNP, were working in Jack's lab with catecholamines and phenylethanolamine-N-methyltransferase (PNMT). It was a natural fit to continue my research on aggression and biogenic amines in that environment. So, during my residency, while I was seeing patients and taking call, I continued work with tricyclic antidepressants and aggressive behavior, as well as looking at second messengers with cyclic AMP that Elaine Orenburg was researching. I also examined the effect of caffeine and other thioxanthenes on rodent aggression, while I completed my psychiatric residency.

TB: You certainly accomplished a great deal during three years of residency.

BE: I also learned a great deal; I was looking forward to working with aggressive and violent patients and trying to understand their behavior in the context of their biology as well as their environmental stressors. During my residency at Stanford, Leo Hollister was also there. I recall one of my first days on call. I was asked to consult on a patient with scleroderma, who was taking tricyclic antidepressants. The medical service wanted to know whether this patient could continue with the medication since it was anticholinergic. I hadn't the faintest idea as to how to answer the question. In Palo Alto, when asked a clinical psychopharmacologic question you couldn't answer, you called Leo Hollister. That was my first contact with him. He was very gracious about being

pestered by a first year resident and said go ahead and tell them it's better to treat the patient for depression.

There were a lot of resources in Palo Alto, not only on the biological side. I had the privilege of working with the Hilgards, particularly with Josephine Hilgard, and learned from her psychoanalytic skills. I worked with Irv Yalom, who was my group therapy supervisor. All that time, either to the detriment or to the benefit of what I was doing, I kept one foot in the clinical camp and one foot in the laboratory.

TB: After all that learning and research what was your next move?

BE: At the time I completed my residency, which would have been in the summer of 1975, there were a number of chairs open and recruitment didn't seem to be heading to where I wanted to live. Consequently, I remained for another year at Stanford, funded by a Kennedy Fellowship in medicine, law, and ethics. This was a fellowship that the Kennedy-Shrivers, Eunice Kennedy in particular, had created. I took some ethics courses at Berkeley, worked with the bioethicist Al Jonsen at UC San Francisco, and audited some law courses at Stanford. All this was done with an eye towards moving into clinical research with aggressive and violent patients and having sufficient legal and ethical underpinnings to proceed in a reasonable way. During this time, at Stanford, Arnie Mandel put together a symposium on aggression which was my initial exposure to the ACNP. The first meeting for me was in San Juan, in 1973. I presented much of the work that I had done at the NIH and some that I had continued at Stanford.

TB: Where did you go after this additional year at Stanford?

BE: At the end of my fellowship year, I looked at a number of departments of psychiatry, including the University of Wisconsin. Madison felt comfortable as a new Midwestern home. The department and graduate school was generous in funding my start-up and my salary was "hard money" as Chief of Psychiatry at the affiliated VA hospital. So my wife, I, and our two children made another move which felt much closer to being "back home."

In Madison, I established a Laboratory of Behavioral Neurochemistry, looking at biogenic amines and second messengers involved with aggressive behavior, utilizing rodent models of aggression. Initially, I had a Pakistani biochemist, Asaf Qureshi, working with me and subsequently one of Paul Greengard's post docs, Linda Hegstand, became the biochemical

director for our laboratory. We had technical and post doc support during those years. Kathy Kantak, who went on to a faculty position at Boston University was part of our lab.

TB: What lines of research did you work on in your new environment?

BE: We continued the line of research with aggressive behavior, working principally with rats and to some degree with mice. We studied primarily predatory and defensive affective aggression. We examined enzyme systems, such as tyrosine hydroxylase, in attempting to localize where biogenic amine affects were initiated. We did a fair amount of work with dietary restriction and tryptophan deficiency, showing that no matter how you deplete serotonin, by p-chlorophenylalanine, neurotoxins, electrolytic lesions of the raphe, or by a tryptophan-deficient diet, you can push the aggression system(s) in brain to enhance aggressive behavior. We looked at receptor systems and showed that an alteration in β -adrenergic receptors led to a correlative change in aggressive behavior. We demonstrated that if you create a super-sensitivity of β adrenergic receptors and then withdraw the β -blockade, for the first 48 hours, you have more super sensitive receptors and you have an increase in defensive aggressive behavior.

TB: What were the implications of your animal research for human behavior?

BE: Not all the laboratory changes we observed translate directly into clinical correlates. Certainly, we do not have evidence that patients discontinuing their β -blocker treatment for hypertension become aggressive. Similarly, though we demonstrated an increase in defensive pain-induced aggression in the rat with chronic antidepressant treatment in docile Sprague Dawley rats, we do not generally see this in patients treated with antidepressants. Though, there are a couple of papers reporting this in the human literature.

TB: Were you trying to find out where the differences between animal and human behaviors come from?

BE: We were trying to look at a balance between neurotransmitters. We had the sense that the serotonin system functioned in an inhibitory manner in a number of different rodent models. We also felt that increased catecholaminergic, noradrenergic-turnover facilitated, or increased, defensive aggression. We had replicated Jon Stolk's findings that the alkaline metal cation rubidium increased aggression, as did immobilization stress and sleep deprivation stress. All of these behavioral findings were associated with increased norepinephrine turnover. There was the sense that in organisms with enhanced catecholaminergic activity, certain types of aggressive

behavior would be increased. This adrenergic story was much less clear than the serotonin story. The research work continued with VA and NIH funding. During that time, investigators working in the area of aggression research were concerned about the scientific and political milieu for such research. Utilizing my bioethics background, I undertook a National Science Foundation funded study of aggression, looking at whether research in this area was being constrained on the basis of ethical or political forces. This was in the period between 1976 and 1980. The outcome of that study demonstrated that in those times, there was no particular problem. Institutional Review Boards (IRB) were developing, but did not appear to be affecting, preclinical research.

TB: Did some of the ethical concerns limit your own research?

BE: During that time I continued to, within the VA system, see a number of aggressive patients. We looked towards setting up protocols to study these behaviors. This was really difficult because of the issues of informed consent and because of the episodic nature of serious or intense human aggressive behaviors. Consequently, most of my clinical work took the form of consulting and collaboration. During this time, I was asked to see a patient with Cornelia deLang syndrome. He was a mentally retarded young man, who engaged in a great deal of self-injurious behavior. His clinicians had measured whole blood serotonin, which had been reported to be altered in some mentally retarded patients. His was significantly low. The clinicians asked for consultation in managing his behavior with available resources. At that time, tryptophan was still a food product available at health food stores. In the pre-SSRI era, the only serotonin enhancing agent with significant specificity was trazodone. So, we suggested enriching his diet with tryptophan and treating him with trazodone. When this was done, the patient showed a major increase in his whole blood serotonin levels and his clinicians could document that his self-injurious and aggressive behavior significantly diminished. We published this correlation as a letter in *The Lancet*. Serotonin in mentally retarded individuals still appears to be an under researched area, including the phenomenon of abnormal peripheral levels of serotonin. It appeared to us, at this time, that the most feasible manner of clinical exploration of human aggression was through natural single subject experiments occurring in the clinic, much as this situation materialized.

TB: Were there any other reports of the use of trazodone in aggression?

BE: Our trazodone effect was in conjunction with the use of tryptophan. However, there have been other reports in the literature, particularly in geriatric populations, using trazodone to

attenuate aggressive behavior. However, placebo controlled studies are, I believe, non-existent. Even with fairly familiar clinical situations such as delirium, where we use trazodone with small doses of atypical antipsychotic agents, controlled studies have yet to be completed.

TB: What was the reason that you left eventually Madison?

BE: The difficulties in implementing clinical research with seriously aggressive patients, funding constraints in the 1980s at the NIMH, and personal issues all were involved in my decision to close my behavioral neurochemistry efforts at the UW. I went through a divorce at that time, which takes a lot of energy. In conjunction with remarrying, I inherited not only a new wife, but four stepchildren. Now we're talking about a total of six children. All of this took a fair amount of energy away from my research. Coincident with this was an academic offer to my new wife, an appointment at UNC in Chapel Hill. So we moved.

David Janowsky, a member of the College, was chair at UNC and Bernie Carroll, also an ACNP member, was chair at Duke when I approached the move. I talked with both of them as colleagues and co-members of the college. David really had the best opportunity for me to continue some of the clinical work on aggressive behavior by taking on a role as Medical Director of one of the state hospitals, Dorothea Dix Hospital in Raleigh. This hospital had one inpatient program of 40 to 50 beds for psychiatric patients who were repetitively aggressive. During that time, I was also consulting with pharmaceutical houses that were attempting to address the issue of aggressive and violent patients.

TB: What line of research did you pursue in your new setting?

BE: There is a problem with American psychiatry in that we can diagnose depression as an affective disorder and we can diagnose thought disorders, but we have no nosology for incorporating into clinical practice something that clinicians struggle with all the time, namely the affective disorder that incorporates aggressive and destructive behavior.

During those years in Carolina, we attempted to address that issue outside of the DSM. We published papers on what we called the Carolina Nosology for Destructive Behavior, attempting to focus on the problems of a nosology for human aggressive behavior, a task that addressed biology, typology, and other differing elements. Is clinically relevant aggression in a particular patient associated with abnormalities in biogenic amines? Is it associated with epilepsy? Is it driven by social stressors? We posited that with a clearer description of clinically relevant

violent behavior, the creators of the DSM, or even leaders within the FDA, would allow for more than just a single diagnostic category of Intermittent Explosive Disorder. We live in a medical culture that affirms that if a disorder doesn't exist, then there is no attempt to understand or treat the condition. Research monies are limited and the pharmaceutical industry does not focus on it. Clinically relevant aggressive behavior, again, becomes a neglected child of medicine.

TB: Did other clinicians or researchers follow up on your concerns?

BE: Despite the championing of a research diagnosis for aggressive behavior by such as Coccaro, of our College, this has continued to be a durable, unmovable problem. During those years I was a consultant to Duphar Pharmaceuticals in Holland. They were researching in their preclinical labs a class of compounds called "Serenics." These were 5HT_{1A/1B} agonists. Duphar wanted to study these drugs in an aggressive clinical population. They packed me off to the FDA in the US for a meeting to determine how they could best demonstrate the efficacy of these agents and get them eventually marketed. It was a very disheartening meeting at the FDA with Paul Lieber. He essentially said to Duphar that you need to have a disease, not a symptom. Even though we treat hypertension, even though we treat angina, even though we treat headache, for "aggression" we need to have a disease. He illustrated how Upjohn had assisted in developing and essentially created Panic Disorder as the disease for treatment with alprazolam. He took the problem one step further into the political arena and indicated, that in this country, it would not be politically feasible to create a disease hallmarked by aggressive behavior and market a product targeted for it. My read about this was that it was un-American to treat aggression with a drug. In all honesty he did not say this directly. I believe he really meant that it was un-American to treat assertive behavior with a "pill" and this would be politically unpalatable.

TB: What was the outcome of your visit to the FDA?

BE: Duphar packed up their bags and stopped the idea of developing or researching these drugs in the United States. They attempted to show efficacy in European populations but my understanding is that they had great difficulty with their control placebo populations and the agents were never developed. Since then, we only see an occasional poster on valproic acid or aripiprazole targeting clinically relevant aggressive behavior. Coccaro has done some work with SSRIs. However, without a clear "disease," there is no clear research mandate and no bona fide treatable population for Pharma to market to. This field, in contrast to research on the mental

health problems of HIV or autism, has remained stagnant. The energy for one investigator or institution to develop a sustained effort in this area has not been forthcoming. Folks, who publish in this area, have continued to do so by virtue of having some other funding stream where they can piggyback this kind of research. This has been very problematic.

TB: What did you do next?

BE: Even though Carolina is a very beautiful place, we decided that we really were Yankees after all. I was offered the Chair of Psychiatry at Temple in Philadelphia and my wife, who is a Ph.D. attorney, was offered a position at the law school. We thought it would be great to return north and we moved to Temple before I had the time to develop the clinical research at UNC and Dorothea Dix Hospital. Time may have been a factor, but it also seemed to me that the “writing was on the wall.” Bringing to fruition the dream I held for a research program, geared to the study of clinically relevant aggressive behavior, was not likely to happen given our current clinical and political environment.

TB: Before moving to Temple you completed the Carolina Nosology.

BE: We did develop the Carolina Nosology for Destructive Behavior, using “destructive” as more politically palatable than “aggressive.” It’s a multi-axial nosology, which gets cited from time to time, when clinical aggression gets cyclically resurrected. We then moved to Philadelphia. It is now 1990.

TB: What plans did you have for continuing your research?

BE: As you note, I did not move my behavioral neurochemical lab from Wisconsin to UNC. I did piggyback some rodent research onto the work that David Janowsky was doing and that a Fogarty Fellow of mine, Olgierd Pucilowski, was doing after he moved to UNC. During those Carolina years we did some work with aggressive behavior in alcohol preferring strains of rats and some work with calcium channel blockers. However, I clearly was shifting toward administration and clinical work.

TB: How did this and your background equip you for your position at Temple?

BE: The department at Temple had been predominantly a teaching department for medical students and, to some degree, residents. With the exception of Charlie Shagass and Donald Overton, also a college member, the department had a more public health, or community mental health vision with a limited biological and psychopharmacologic research perspective. There was

a lot of work to do to change the medical school teaching and bring Temple medical students face to face with the changes in behavioral neurosciences that were impinging on psychiatry. We remade the first year psychiatry course into a neuroscience course. There now was clearly “testable” content. Unprepared for this “new psychiatry,” a third of the medical students failed because they thought this was “just psychiatry.” They believed you only had to learn how to “feel” about patients, instead of learning about receptors, neurotransmitters, and brain regions. This was a time of significant transition, and the medical students in subsequent years came along.

TB: Were you able to pursue or encourage any research as Chairman?

BE: We continued to try to enrich the research aspects of the department and urged our residents to do some scholarly work and present this at a Grand Rounds. Even if this revolved around a case report, it was geared to review the literature and consider publication.

Funding issues in psychiatry, for any department of psychiatry, were excruciating during those years. They still are. There were issues of mobilizing complacent faculty to see patients and to generate revenue, if they were bringing in their salary on a research grant. The “free ride,” or the payment for teaching exclusively as a salary support, was ending in academic psychiatry. There was a great deal of angst during those years. It was very difficult, not just for me, but for all department chairpersons, to maintain departmental fiscal survival while trying to meet the departmental mandates for teaching, for making new discoveries or contributing to our medical knowledge base, as well as provide top notch, conscientious care for our patients.

During that time, I didn’t have the time to do controlled studies, to get outside funding for research. However, I consulted at a residential facility for clients with developmental disabilities. Temple operated this facility and we saw a fair number of aggressive, mentally retarded clients. From that experience, though not published, were some interesting single case studies using β -blockers as well as SSRIs in autistic, aggressive patients. We would have a steady baseline of aggressive behavior cataloged by the psychologists on the units, then introduce the pharmacologic agent and show a reduction in aggressive behavior. If the medication had to be withdrawn for a side effect or if another clinician discontinued the medication, we would usually observe an increase to baseline of the aggressive behavior. We could demonstrate good correlative findings.

We also had a very interesting “natural discovery” at that facility, where the dentist refused to do dental care on these patients unless they were anesthetized for fear of being bitten. The

parents would not consent to general anesthesia, so these clients had very bad dentition. A new dentist came to the facility and agreed to see them as long as they didn't bite her. She took care of their dentition, and remarkably, when they had their root canals repaired, the aggression ceased. With a medical student, we went back to these patients and showed, using an estimated pain scale from the School of Dentistry, that there was a statistically significant correlation with what would have been the expected pain for these nonverbal patients and their aggressive behavior. This did underscore what we know clinically and teach, namely, that there are other interventions besides biochemistry or pharmacology for modifying aggressive behavior. Academically, during that time, I mostly did reviews of the literature. I also served on a NIMH study section in the areas of PTSD and aggressive behavior.

TB: So your time at Temple was more in administration and teaching. Where did you go next and were you able to return to research?

BE: After seven years as Chairman in Philadelphia, both my wife and I felt it was enough and we returned to Madison. So, I am back in Madison at the University of Wisconsin. I am no longer doing aggressive behavior research. I am mostly teaching and providing clinical service. I head the consultation/liaison and emergency psychiatry hospital services there.

I suppose some people would say, well, all of this research training and why haven't you persevered? Why aren't you publishing papers? When I come back to meetings such as the ACNP, I ask myself that question. At the same time, I really believe that the research portion of my life allowed me to become both a better clinician and teacher to a new wave of predominantly generalist psychiatrists. It is critical to make them aware of how to read research papers and how to use clinical situations as a way of triggering curiosity and posing questions that can then be taken into either the research or basic science laboratory for study. I'm having fun with that right now.

TB: When did you leave Temple?

BE: We left Philadelphia in 1997. For a period of time, there was a hiatus in my academic career. I'm not certain that it is obvious on my current curriculum vitae but maintaining one's self in the academic arena can be difficult, especially if you only want to live in one city. I did not have an immediate jump back to the UW faculty in Madison. I did some insurance consulting during the interim. This was a strange world to be in for an academic psychiatrist. But I followed

another ACNP member, Barry Blackwell, into a behavioral health medical directorship, for a company based in Milwaukee. Subsequently, a position opened back at the UW and I returned full time, in 2001. And now it is almost 2004.

TB: Before moving to that, would you like to say anything further about your research and publications?

BE: We published some papers much like Mike Sheard's group at Yale. Michael was another person who was a psychiatrist, worked with animals, but also worked with patients. He published significant work with lithium in both rodents and aggressive prisoners. He, too, had difficulty with American science and morality being in conflict. I recall him telling me about his proposal to treat male domestic abusers with lithium. He went to the Yale IRB to do this; this is apocryphal, but I think it is accurate. He was told by the community representatives on the IRB that domestic violence is a "moral issue," not a "biological one." These abusers are bad people and clinicians shouldn't be helping them or giving them a "biological" excuse. They should go to jail. The community representative to the IRB contended that studying lithium in this population was inappropriate. I don't believe that this study has ever been done, although a number of us have used SSRIs, lithium, or other agents, untested in blinded studies of domestic abusers, and found this helpful without obviating the abuser's legal or moral responsibility but helping them to conform their behavior to the law.

We also did studies with lithium, rubidium, cesium, and the alkaline metal cations. The two that really altered aggression in our pain-induced model were, of course lithium, and remarkably rubidium. It would have been dramatic to have had the ability to videotape the behaviors we observed. For example, in terms of brain lesions, a rat with large lesions of the septal nuclei is a very irritable rat. You can blow on this rat and it jumps out of the cage at your face. In terms of alkali metal cations, rubidium-treated rats are incredibly aggressive animals, an effect first reported by Jon Stolk, a past member of the ACNP. What occurs in the brains of these animals to change their affect, to make them so aggressive? I don't think we know yet, although we do know that norepinephrine metabolism is increased.

Ron Fieve from New York Psychiatric Institute had attempted clinical protocols with rubidium as an antidepressant, as it had been used in uncontrolled treatment in Russia. Since its therapeutic effect for depression at safe dosing was not dramatic, the research did not proceed. I

don't believe it was ever used at doses comparable to our animal studies, so to my knowledge there was never any report of it inducing marked irritability. It is fascinating and remarkable that you can give as simple a compound as a chemical salt to an organism that has been bred for generations to be docile and induce dramatic irritable and aggressive behavior.

TB: But you never reproduced these effects in patients?

BE: I have worked with repetitively aggressive individuals, whose closest DSM diagnosis would be intermittent explosive disorder. I have worked with mentally retarded folks. I worked for a period of time as a consultant to the Philadelphia Geriatric Center, treating aggressive, demented, adults. For whatever reason, be it administrative demands, my conscious or unconscious choice, my abilities or my inabilities, I did not commit those patients to systematic study such that I could publish it in the academic literature. I did publish some open case reports in the *American Journal of Psychiatry* and in *The Lancet*.

TB: You were clearly frustrated in your research efforts. What might have made a difference?

BE: I believe it really would have been helpful for moving the field along if there could have been an endowed chair for aggression research where NIMH or some other organization funded a responsible investigator in a program to study a clinical condition that needs to be addressed. Fund it substantively for five years and see what comes out. The issue is of a magnitude sufficient to justify this approach. We essentially did this for AIDS and we did it for AIDS dementia at the time that HIV was becoming epidemic.

TB: What do you think, why this did not happen in research on aggression?

BE: One of the major impediments to such clinical research is the issue of informed consent. Somebody would have to provide informed consent by proxy for many of these patients, particularly the developmentally disabled or the demented. I believe there could have been greater research contributions to the field and to the practicing clinician if there had been a societal mechanism to oversee ethical research around this topic, weighing the risks of research with the benefits of attenuating aggressive behavior that often leads to more restrictive living conditions. Right now, clinicians have few controlled clinical studies to rely on in the treatment of the destructive behavior of their patients. They are essentially flying by the seat of their pants.

TB: Are there valid, reliable measures of aggressive behavior, such as the Buss-Durkee aggression inventory?

BE: The Buss-Durkee inventory doesn't measure the assaults. Probably the one that gets used the most is the Stuart Yudofsky's Overt Aggression Scale. Coccaro modified that. Our Carolina Nosology was a way of compartmentalizing or cataloging patients so that you don't mix the demented aggressive patient with the mentally retarded patient, the patient with autism or the aggressive patient with mania. These populations need to be separated so that if you are going to do pharmacotherapy or behavioral interventions, you don't lump everything together. Clinically relevant aggressive behavior is a heterogeneous issue.

TB: Do you consider aggression as a condition co-morbid with a specific disorder, or do you consider it to be independent from diagnosis?

BE: Certainly it can be co-morbid. When I was working with the developmentally disabled population, I evaluated a young woman whose mother had just died. This client was non-verbal. She looked depressed, and she looked as if she might fit Fava's aggressive depression characteristics. I had been asked to see her because of temper tantrums and assaults toward peers and staff. We started her on trazodone which we had been using in this population. Well, we flipped her into mania. The next week, when I returned to the facility, she was running around and singing songs. She wasn't crying anymore, but she was equally as assaultive. What was needed for her, as her diagnosis was clarified, was a mood stabilizer; to have her primary bipolar diagnosis treated first.

TB: Do you think trazodone should be systematically studied in any particular disorder where aggression is a common symptom?

BE: I used a lot of trazodone in geriatric patients. It would be an interesting and useful study, particularly in patients with Lewy body dementia, where there is a risk in using typical or atypical antipsychotic agents. Even to take a population into an open study could be valuable. But the probability of obtaining funding is quite limited given that trazodone is off-patent and the agent doesn't fit a theoretically defensible construct to garner federal funding.

TB: Does the aggression of a schizophrenic patient differ from the aggression in a geriatric, demented patient in responding to trazodone? Would you think that aggression in a schizophrenic patient would respond better to another drug?

BE: Well, Jan Volavka tried a study with tryptophan supplementation in schizophrenia. This was done before tryptophan was taken off the food market. If I recall the paper correctly, one or two

patients responded positively, but most of them did not. He did not do that study in combination with other drugs that might have made tryptophan more effective, such as we did in our *Lancet* paper.

TB: So both you and Volavka used tryptophan supplementation to increase serotonin to control for aggression in schizophrenia.

BE: However, its toxicity, secondary to impurities of tryptophan halted this approach.

TB: What drugs were you using in your animal research for controlling aggression?

BE: We worked mostly with drugs to modify neurotransmitter systems. So we were particularly involved with ways of enhancing or depleting serotonin and noradrenergic systems. That was the focus of the lab. We also looked at whether strain differences or other influences, such as environmental mental stress, could push these systems in a way to change aggressive behavior.

TB: What animal models did you use for studying aggression?

BE: We worked with Karlis' model of predatory aggression and mouse-killing behavior. A certain number of rats will spontaneously kill mice. This can be modified through brain lesions or brain chemistry changes. There is also a murine model of cricket-killing. Similar to rats and mouse-killing, mice will kill crickets.

We also worked with pain or shock-induced fighting in the rat as a model of affective, defensive aggression. And we began to incorporate Micek's intruder model of affective offensive aggression, but this was just at the time I was moving to Carolina and I did not reestablish my lab there. We also carried out general rating scales on more naturalistic behavioral situations, but most of our publications focused around pain-induced or shock-induced fighting.

TB: Weren't you involved in conditioning research?

BE: We did not do conditioning experiments in this model. The closest we came, and it really is not conditioning, was the work I did with Redford Williams at the NIMH. Redford was a behavioral internist interested in blood pressure, hypertension, stress, and emotion. He proposed we record blood pressure in these rats using a non-invasive tail blood pressure measurement. Interestingly this led to a paper in *Science*. When the animals are paired and receive foot shock, their blood pressure goes down, probably due to a peripheral vascular effect. This is highly replicable and statistically significant. However, if you take these same rats and give them the same foot shock alone in the cage they do not have the coping behavior of fighting and the tail

blood pressure goes up significantly. The physiology and chemistry of these two responses is different. The increase in tail blood pressure is linked to the adrenal gland. Adrenalectomized rats do not show this effect. The decrease in tail blood pressure is a central effect and can be blocked in the centrally catecholamine-depleted rat that is treated with 6-hydroxydopamine. Even more fascinating to us, was the observation that if you put the rat in the cage, alone, and give it just enough shock to induce a flinch, you see the same increase in blood pressure. If you put two rats in the cage and provide a foot shock sufficient to induce a flinch, you see the opposite effect, reduction of blood pressure. This serves as a prototype or model that the social environment of an organism makes all the difference in the world, not only in the context of behavior, but also, in terms of their physiological response. How little we know about how these social cues affect our human physiology and how this differs from individual to individual!

TB: Have you done research in the non-pharmacological influences on human aggression?

BE: No, we just did it in the context of our animals. Clearly, however, when you teach about managing aggressive behavior in clinical populations, you need to look at the environment and what's happening to the organism within that environment. Let me give an example that might illustrate this. Because of my interest in aggression, I have done forensic consultations and was seeing a prisoner in Wisconsin who was an arsonist. He had previously been treated with lithium but discontinued it and set another fire. Under Wisconsin law, he was clearly responsible for his action and was not going to be excused by the State. The same day that I saw him, the *Archives of General Psychiatry* came out with an article by Matte Virkunen from Finland, reporting low CSF levels of 5-hydroxyindoleacetic acid (5HIAA) to predict recidivism in arsonists. I wasn't going to be able to assay this gentleman's 5HIAA in cerebrospinal fluid (CSF), but I would bet he had a low level and would fit into Virkunen's high risk population.

This leads us to the issue of how much of our behavior is driven by our biology. It even takes you back to Original Sin and Predestination. What does it mean for us as humans to think and talk about free will or morality and at the same time know that there are biological processes that drive us to more impulsivity, deliberation, or anxiety, making it easier or more difficult for us to function in a "moral environment." I don't have an answer to this complex problem, but I think this is one of the great human questions. As one gets older, one spends more time pondering these questions.

TB: Do you think biological measures, such as 5HIAA, would help identify who is at risk for aggression?

BE: Low levels seem to put you at risk. The question is, shouldn't we know about the biology of our patients or even our prisoners. Marku Linoilla, another, now deceased member of the College, claimed it was criminal not to know what the CSF level of 5HIAA is in any depressed or violent patient because it is a significant risk factor for completed suicide and serious violent behavior. Why shouldn't we evaluate that any less than measuring elevated blood pressure in assessing risk factors for health and safety. Just as with hypertension, shouldn't be 5HIAA level an indication for early medical intervention?

TB: Is there sufficient evidence for that?

BE: I believe it would be a reasonable medical and social project to assemble and follow a population longitudinally and measure the predictability of low 5HIAA on human behavior. But in this country, we have a lot of difficulty putting needles into people's backs, especially those who may be violent and may choose not to consent. So, it would be wonderful if we could develop non-invasive techniques to measure compounds like 5HIAA in the CSF. We do spinal taps in children with meningitis and the lifetime risk of harm due to aggression may be just as grave in individuals with low levels of 5HIAA.

TB: Do you have any suggestion about selecting medication to treat aggression?

BE: It depends upon the individual. Our social database is crude right now. Coccaro's work suggests in people who have an intermittent explosive disorder, serotonin-enhancing agents like SSRIs can attenuate their aggressive behavior. This is also consistent with Mike Sheard's work with lithium. He suggests that the effect may not be directly on "anger" per se, but rather on the impulsivity and the "hair trigger" evident in certain individuals. In conversation, he noted that aggressive prisoners on lithium reported that they were just as angry but had some time to think about whether they wanted to go into solitary confinement or not, inhibiting their aggressive behavior.

The literature concerning brain-injured patients treated with high doses of β -blockers, such as propranolol, is also compelling, probably also affecting impulsivity more than anger. I've seen this intervention effective for patients that have preexisting head trauma. There is compelling literature that argues for the use of low doses of antipsychotic agents, particularly the newer

atypical agents, in managing aggressive behavior in clinical populations. We would do better both with compliance and demonstrating efficacy if we characterized these patients with greater specificity. This comes back to the fact we don't have a nosology within DSM to define aggressive patients in day to day clinical practice. We don't know which populations would do best with behavioral interventions alone, or in combination with pharmacotherapy, such as in the treatment of post-traumatic stress disorder. Until we have homogeneous populations in which to test interventions, it becomes very much "catch as catch can."

TB: Let's go now to some of your most recent activities.

BE: I'm not doing research now. I miss that, but I'm also very busy clinically, and I'm busy with ten grandchildren, so there's a personal life that is very rich. Certainly there are some natural opportunities. On the consult service we've encountered several patients with aggression and Lewy Body Dementia. I should be thinking more of developing and using single patient protocols for psychopharmacologic discovery. However, the reality is that those of us in the clinical arena are very time-strapped providing services to poorly funded programs.

I do a lot of consultation with the transplant teams. We see psychiatric and behavioral problems with liver, heart-lung, and kidney-pancreas transplant patients. I don't talk with my transplant colleagues about reimbursement. They work very hard; but American medicine is set up to reward "procedures" which are substantially more remunerated than psychiatric practice. It would be delightful if the funding resources were greater, so that I could share my role with a colleague. This would allow me time for scientific development and protocol writing to improve the clinical condition of the aggressive patients we see and more effectively guide our clinical interventions.

TB: Let me switch topics. When did you join ACNP?

BE: I don't remember. I suspect that it was in the late 1970's. Leo Hollister and Jack Barchus were my main sponsors. As I said earlier, Arnie Mandel invited me first to the College, in 1973, to participate in a plenary session on aggression.

TB: What would you like to see happen in the future? You mentioned a couple of things you would like to see occur.

BE: American psychiatry needs to come to terms with clinical reality. There are many patients who are disenfranchised. They are being treated at more intense levels of care, more restrictive

levels of care, than they would need to be if their aggressive behavior were in better control. American psychiatry, the APA and the NIMH, need to recognize this is a significant clinical and human problem with major economic and personal costs. It is not a criminal problem. There is a criminal problem too, but I am referring to the clinical problem. These patients are being sometimes appropriately, sometimes inappropriately, but most of the time not at all, treated for their aggression, which DSM doesn't recognize as a disorder. This is a disorder that alters lives, which may already be impaired by head injury, mental retardation or by dementia. As a clinical problem area, psychiatry and the whole of behavioral health need to look at this. They should recognize it and develop a moral, ethical, and clinical strategy for intervening. This requires the organization of information we already have. It also requires testing hypotheses to improve these peoples' lives. It is very difficult because many of them cannot provide informed consent. If you turn that around, though, why should a person who cannot provide informed consent be disenfranchised from research opportunities that a person with a panic or depressive disorder has access to? I think that is not only unfortunate, but morally wrong. We should develop some type of national effort. This is not mind control. It is not social control. But it could benefit a very large population, who are isolated, disenfranchised, and often imprisoned by their aggressive behaviors.

TB: That is a passionate summary and I think we have probably covered everything we need to. Thank you very much.

BE: Thank you.

17. HANS CHRISTIAN FIBIGER

TB: This will be an interview with Dr. Hans Christian Fibiger¹⁹ for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College in San Juan. It is December 8, 2003. I am Thomas Ban. If you could start from the very beginning and tell us something about where you were born, something about your education?

HF: I was born in Copenhagen, in 1943, and spent the first five years of my life in that beautiful city. My parents decided to move to Canada, in 1948, probably primarily because my father had five sisters in Copenhagen that he needed to get away from! But, seriously, my parents always told me the reason for moving to Canada was that they felt the future for the kids would be better in Canada than it might have been in Denmark. And, as I think back on it, it was the right move for me and for my sisters and brothers. So, in 1948, we got on a big ship in Sweden and made the trip across the Atlantic and landed in New York. Then, we took a train to Montreal, another train from Montreal to Vancouver, and ultimately ended up in beautiful Victoria, British Columbia. That is where I spent my youth and went to school. We had a lovely home. Victoria is one of the most beautiful cities in North America, and I had an absolutely idyllic childhood. I continued my studies at the University of Victoria, where I enrolled in 1960, and unfortunately, did not graduate until 1966. I spent six years as an undergraduate because I kept changing my mind about what I wanted to do in life. My parents told me I had always been good at math, and therefore, I should become a chartered accountant. As I looked into that opportunity, I decided quickly that wasn't the right life for me. I started to read Freud as a high school student. I became very, very interested early on in the human mind and trying to understand its dynamics. And like so many other people in that era, the more I thought and read about it, the more it became evident that the key to understanding the mind was to understand the biology of the human brain. So, during my undergraduate training, I eventually shifted to major in psychology and chemistry and graduated with honors in 1966. I then wanted to go to graduate school, applied to a number of places, and

¹⁹ Hans Christian Fibiger was born in Copenhagen, Denmark in 1943. In 1948, he and his family immigrated to Canada. He completed his undergraduate degree in the University of Victoria in British Columbia, Canada and graduate studies Princeton University. He returned to the faculty of the University of British Columbia for almost three decades before moving to a leadership position in industry, first at Lilly and then, at Amgen. San Juan, Puerto Rico, December 8, 2003.

finally decided to accept an offer at Princeton. That turned out to be a very good experience for me as well. At the time I arrived in Princeton, I was interested in physiological psychology, but the advisor I ended up with was a person who had nothing to do with physiological psychology. He studied infant-mother interactions, and so I spent a good part of the first year behind one-way mirrors watching mothers and infants interact and scoring various dimensions of their behavior. Then, there was an opportunity that came up in the Department of Psychology to work with Dr. Byron Campbell, who suddenly received a very large grant in psychopharmacology from the National Institutes of Mental Health and was looking for new graduate students. I quickly knocked on his door and asked whether he would consider me to work in his lab. He graciously agreed, and I ended up spending the next three years with him. I took a year off from graduate school, tragically, because I had a young brother who, at the age of 16, died of leukemia. But I went back to Princeton and completed my degree in what was, essentially psychopharmacology, in 1970. I had a very good experience at Princeton and made some great friends while there.

TB: Could you tell us something about the research you did with Byron Campbell?

HF: We were studying the effects of psychoactive agents on rat behavior as a function of age; it was developmental neuropsychopharmacology. Dr. Campbell had an interest, for a long time, in developmental biology from a behavioral perspective, but it was an area of research he himself did not know much about. So, we learned together, and perhaps, through no choice of his own, he let the students train each other, which was a great way to learn, I came to understand. In 1970, I left Princeton and accepted a post-doctoral position in Vancouver to work with Drs. Patrick and Edie McGeer, who were two very well-renowned neurochemists in the Department of Psychiatry at the University of British Columbia. I also planned to spend half my time with a neuropsychologist, Dr. Harry Klonoff. It was meant to be a joint post-doctoral experience that was funded by the Medical Research Council of Canada. With Dr. Klonoff I was involved in studies that applied neuropsychological batteries to individuals with schizophrenia. We published one of the very first papers on a neuropsychological assessment, using standardized tests, in patients with schizophrenia. That field has grown and expanded enormously, but this was back, in 1970. I remember having heated debates with Dr. Klonoff about whether the reduced test scores really reflected true cognitive deficits as opposed to an inability of these patients to attend to or stay with the test we administered. The deficits were very broad and not specific. Subsequent events have

shown that the cognitive deficits are not just an artifact of a psychotic process, but a true core feature of schizophrenia. I think back fondly on the debates I used to have with Dr. Klonoff about that.

TB: What tests did you use for measuring cognitive deficit?

HF: What we used at the time were conventional neuropsychological tests, like the Benton Visual Retention Test, various subtests of the Wexler Intelligence Scale, etc.

TB: Didn't you use conditional reflex measures?

HF: We didn't; we used just neuropsychological tests. I did, with Dr. Klonoff, one of the first studies on the neuropsychological effects of marijuana. This was during the height of the "marijuana period" in North America. We did an interesting study on how people performed after smoking marijuana in a simulated driving test. That study was placebo-controlled. The subjects would smoke either marijuana or marijuana from which THC had been removed. As one might expect, there were adverse effects on cognitive function. It was interesting to see the number of people who reported getting high when they smoked the placebo. That was a lot of fun.

Most of my time in Vancouver during my post-doc, however, was spent with Pat and Edie McGeer. We did a lot of interesting work together. The McGeers were focused on analyzing human brains postmortem and looking at the activity of various neurotransmitter synthesizing enzymes. They were interested in Alzheimer's and Parkinson's disease. We would obtain fresh brain tissue by an arrangement with the coroner in Vancouver. I remember that we would go and harvest these brains whenever we got a call, in the middle of the night or some other part of the day. We had to get the brains quickly to the lab, put them immediately on ice, dissect them, and run the neurochemical assays. I think we were one of the first labs to show that there was a decrease in choline acetyl transferase activity in the brains of people with Alzheimer's disease. We confirmed the classical studies showing that dopaminergic neurons were damaged in Parkinson's disease and we conducted a lot of animal work during that period. I also studied axonal transport in the central nervous system by injecting microliter quantities of radio-labeled amino acids, which could be incorporated into the cell, synthesized into proteins, and transported up the axon to the nerve terminals. I did this experiment after hours because Pat McGeer thought it was "a crazy idea." When the data worked out extremely well, and I showed him the data, he became very interested and wanted to be a co-author on the paper. What I learned from that experience was to

trust my students and let them follow their instincts. The young, untrained, creative brain often comes up with ideas that those of us who have been indoctrinated for longer periods of time wouldn't think of. I have always managed my students that way and gave them probably more room to operate than others did. It didn't work for every student; some needed more guidance than others. But I always tried to provide as much freedom as they could handle because of my own personal experience as a post-doc pursuing ideas my advisors told me not to, but which worked out well.

After my post-doc with Klonoff and the McGeers, I applied for a Medical Research Council scholarship in Canada. I was offered a position to stay in Vancouver, as an Assistant Professor in the Division of Neurological Sciences, which was in the Department of Psychiatry at UBC. I got my own lab space and was very lucky to get an MRC scholarship that supported my salary for five years. I also was successful in getting funding for my first grant application. That was the initial period of 27 years as a professor at the University of British Columbia.

TB: What was your first research grant for?

HF: The first grant was to pursue further studies on axonal transport in the central nervous system. But, I soon hooked up with a person who turned out to be a long-term friend and colleague, Tony Phillips, who had just joined the Department of Psychology. Tony's interest was in studying brain stimulation and reward mechanisms. He was able to show that by implanting electrodes in certain regions of the brain, animals will work to stimulate that part with small electrical currents. That was the area Tony focused on while I was becoming more and more interested, as an independent investigator, in pursuing the neurochemistry of learning and reinforcement. Tony and I partnered to do some studies into the neurochemistry, neuropharmacology, and neuroanatomy of brain stimulation and reward. We submitted some joint grant applications and began a very productive and successful long-term collaboration which lasted about 25 years.

TB: Wasn't that area of research opened up by James Olds with his findings at McGill.

HF: Yes. We used the technique developed by Olds. It was an area of research Tony had a great interest and expertise in. I had become very interested in intravenous self-administration of drugs as a tool to understand addiction and received a grant from a Canadian funding agency, created due to concern about illicit drug use. I was very lucky to get that grant to study the biology of addiction. It fit very nicely into the work I was doing with Tony Phillips on brain reward

mechanisms from an intracranial self-stimulation perspective. An early result of that work was the discovery made by David Roberts, the first graduate student in my laboratory, that the nucleus accumbens is a key structure in the brain that mediates the reinforcing effects of cocaine. Now, we all know that today; it is well accepted and understood. Dave's work in my laboratory was the place where all that started. We had animals self-administer cocaine and would make very selective six-hydroxy-dopamine lesions in the nucleus accumbens and other areas to study what effect they would have on the cocaine self-administration. To our amazement and delight, it turned out that if you destroy the dopamine terminals in the nucleus accumbens, animals stop taking cocaine, even though they took it before. It's as if they lost interest in cocaine. That discovery has spawned a whole industry in academic research, which is still going on today. But I feel very proud and pleased that work started in my laboratory. We opened up this new field, which was something we felt very good about. Dave Roberts, who is now a professor in North Carolina, and still working in that area, deserves a lot of credit for having done that outstanding research. So, that was one of the things that we did. We did many, many other things as well. My laboratory in Vancouver became a place for interdisciplinary research. We did a lot of work in neuroanatomy, during which we studied the anatomy of the extrapyramidal nervous system using emerging new techniques dependent on axonal transport. My previous interest in axonal transport fit nicely with that new technology. We got more and more into immunohistochemistry and all the modern tracing techniques that exist in neuroanatomy. So, we had a long project studying the detailed connections of the extrapyramidal system. We also were amongst the first to map the distribution of cholinergic neurons in the brain. It culminated in a very big review paper that I published in *Brain Research Reviews*, in which I synthesized the research findings in this field. I think that was a useful contribution. There were many other labs working in the same area and I think we helped define the anatomy of central cholinergic neurons, which have become of interest because of their role in Alzheimer's disease and in arousal function. We became very interested in understanding the role of the locus ceruleus, a noradrenergic nucleus that sends projections widely through the forebrain and has descending projections to the spinal cord. We did a lot of work trying to understand the role of those projections on behavior. I think that was very important research. There was a big debate, at the time, in which Larry Stein, a member of this College, and I were involved. Larry felt that the noradrenergic system, originating from the locus ceruleus, was a very

important reward-related system; we debated this point intensely. I think history has shown Larry was wrong; that the locus ceruleus is not significantly involved in reward mechanisms. Now we know, partly on the basis our work and partly on the work of many others, that the mesolimbic dopamine system, starting in the ventral tegmental area and enervating the nucleus accumbens, is the key component of the neural circuitry of reward. The other work we did on the locus ceruleus and the so-called dorsal noradrenergic bundle got me involved in my first, and hopefully last, case of scientific fraud in my laboratory. I had what looked to be a profoundly gifted student whose name was Steve Mason, who received his Ph.D. with Susan Iverson in Cambridge. He came to my lab to do a post-doc. Unfortunately, it turned out that Steve Mason published some data that couldn't be replicated. After he left my lab, I spent part of the next three years publishing retractions and redoing many of the experiments. In those days, it wasn't as big a deal as it is today. Today, and rightfully so, scientific fraud is something the scientific community takes much more seriously than it did 20 years ago. But that was a very disturbing period that we had to try to clean up. And, of course, I did my very best after that to make sure that Steve Mason never got a job again in science. My view of scientific fraud is that that is the capital crime of our business. It deserves capital punishment, meaning you don't work in science again.

After that period, we did a lot of neurochemistry. We were among the first to get into brain microdialysis, in a big way, where we could study neurotransmitter release in awake animals. We did some really nice studies showing that you can actually study neurotransmitter release in animals that are performing different tasks. One of the most enjoyable experiments we did, was to look at dopamine release in the nucleus accumbens during various stages of sexual behavior in male rats. You could watch dopamine release in the nucleus accumbens go up a little bit when a female was introduced into an environment close to the male, and then as they started to copulate, dopamine release would shoot up, showing that this was not just a system cocaine works on, but has something to do with mediating natural reinforcers. We did similar kinds of work with food intake. We also did a whole lot of interesting pharmacological experiments looking at acetylcholine release using microdialysis. That provided us with useful information about what acetylcholine is doing in the brain during different kinds of behavior. It also told us a lot about how you can pharmacologically manipulate central cholinergic neurons.

The last thing that I'll mention, in terms of work we did at UBC, was concerned with immediate early genes, and as always, it was something one of my students brought in. He was a new postdoc, whose name is George Robertson. George had become, as a graduate student at Dalhousie University, very interested in immediate early genes, such as c-Fos. He was interested in continuing some of that work in my lab, and I have to admit that before I met George, I practically knew nothing about immediate early genes. This was an area that was exploding at the time, but an area I had not personally followed. I tried, as usual, to give my students as much freedom to follow their interests, as long as I could be convinced it was worthwhile. And George certainly had. I didn't need much convincing. So what we started to do with this technique was to study the activity of central neurons as reflected by the extent to which they were expressed in c-Fos. With this immediate early gene, you can see changes in either messenger RNA or protein very quickly in neurons activated by some sensory or pharmacological stimulus. We used early gene expression to do a functional mapping of the brain in many different circumstances. One of the things we did was to place animals in environments that caused a lot of anxiety because they had been foot shocked in that environment before. It was amazing to see that when the animals were returned, they were obviously stressed by being back in that environment. You could see the neural circuitry involved light up. We mapped that out and defined some of the circuitry. That nice work was done by a colleague, Charles Beck, a professor from the University of Alberta in Edmonton, who spent a sabbatical in my department. One of the really interesting things that George had done, was to map the distribution of neurons in the forebrain that are activated in vivo by antipsychotic drugs. We could show very nicely that atypical antipsychotics activated a different set of neurons to a significant extent than did typical neuroleptic agents. That work has now been confirmed by many other labs.

TB: Was there any overlap between atypical and typical neuroleptics?

HF: There was some overlap. But the bottom line is that whereas the typical neuroleptic agents targeted the striatum as much as the nucleus accumbens, the atypicals are much more active in the nucleus accumbens, which is quite consistent with their lack of extrapyramidal side effects that are mediated in the striatum. We also showed other differences as well. So the atypicals clearly had a different signature in the brain than do the typicals. This has now become a technique used in the pharmaceutical industry as an assay to guide drug discovery.

TB: Is it used for the screening of new atypical drugs?

HF: Right. We did a lot of other work with immediate early genes, but those were a couple of the highlights, I think.

TB: Wasn't some other work going on with early genes about the same time?

HF: Yes. The immediate early gene work we did was not unique. We didn't discover this technique, but we applied it in interesting ways. And we were amongst the first to understand how you could use this technique to map, in great detail, the activity of neurons in the brain. Another comment I would make is that, in my experience, every laboratory goes through great periods and not so great periods; over 25 years, my lab went through some absolutely fabulous periods and produced some very innovative science.

TB: What year did you become an independent investigator?

HF: I started as an independent investigator in 1972.

TB: How long did you stay at UBC?

HF: Until 1998, so it was 26 years. In 1998, I had an offer to become Vice-president of Neuroscience at Eli Lilly and Company. That was a very difficult decision. My lab was still well funded and we were still doing lots of interesting work. But the question I asked myself, at the time, was how good would I be at doing something else? And one thing that happened during those 26 years, almost inevitably, was that I wasn't as excited about what I was doing as when I was getting started. The arrival is not as interesting as the journey. I had been Acting Head of the Department of Psychiatry for about three years; that taught me I did not want to be an academic administrator. I could have considered in Vancouver to become vice-president of research or something like that, but I wasn't really interested.

TB: When was this?

HF: I acted as head of psychiatry on two occasions for about 1 ½ years each. It was in the 1980s and 90s that I did this. I enjoyed it, but it was not something I wanted to do. The problem with academic administration is that you have responsibilities without real authority. That's not a good equation. If there are tenured professors who are not pulling their weight, or who have gone out to pasture, there is very little you can do, because in the Canadian system, salaries are paid by the university, so they are not dependent on grant funding at all. Persuasion is OK, but it's not a very effective tool to make things happen. So this opportunity at Lilly came along. I got a call from

David Leander, a very senior behavioral pharmacologist at Lilly, who told me they were looking for a Vice-president of Research and asked would I be interested. I initially said no, I hadn't even thought about moving to industry. Then, we had some additional conversations. He finally convinced me to visit Indianapolis and I liked what I saw. There was a terrific group of people at Lilly. The other thing that was happening was my own lab was moving more and more into molecular neurobiology and what I wanted to do was very expensive.

TB: What kind of molecular neurobiology did you want to do?

HF: I wanted to study transcript profiling in primates, because the primate brain is very different from the rodent brain, and I wanted to understand something about gene expression in primates.

TB: Early gene expression?

HF: Right. Using transcript profiling, performed with chip technologies, like affymetrix chips. But it was terribly expensive to do and probably beyond what one could do in Canada, in terms of the level of funding one can get. I discovered, as I visited Lilly, that a company of that size has incredible resources. We could start to do that kind of research, so it was very attractive, and I decide to go to Lilly and try my hand at running a very big organization. Lilly Neuroscience had a research site at headquarters, in Indianapolis, and a research site just outside of London, in a place called Earl Wood, so it was an international operation. Still, it was a very difficult decision. I think anybody who makes the jump from academia to industry always wonders if they're doing the right thing, particularly when their academic life is going just fine.

TB: It made it possible for you to do what you wanted to do.

HF: Oh, absolutely, and as I said, it would have been hard to get the money to do what I wanted in Canada. Eventually, after going to Lilly, we did those experiments. They were very expensive, but we did them. It was tough moving from Vancouver, which is probably the most beautiful city in North America, to Indianapolis, which is a pretty plain vanilla town in the Midwest. But Lilly was a great company and I had a terrific time there. My family enjoyed it in Indianapolis and my kids were in a wonderful school. I have never regretted the decision to try my hand at industry. It was a great time, and I'm glad I did it. In the last last two months, I left Lilly for an absolutely wonderful opportunity to join Amgen, the largest biotech company in the world, and certainly the world's most successful. Amgen called me earlier this year and asked if I would like to come to Thousand Oaks, in California, to head up a new neuroscience department. The goal at Amgen is

for me to build neuroscience into a very powerful force in discovery. I went for a couple of reasons. It wasn't I was, in any way, unhappy at Lilly. There were some things I didn't like, but the overwhelming reason for going was to have a chance to build something in a company that has absolutely outstanding leadership, has lots of resources, and do something different. Hopefully, five or seven years from now I will be able to look back on my time at Amgen and feel that I built something unique and very good; that's certainly my goal.

TB: Before moving into that, could you tell us more about what you did at Lilly? I understood you did some research in early gene expression. What else did you do and how did your research in early gene expression translate into the development of new drugs?

HF: Well, that's a very good question, Tom. Most of what I did at Lilly was manage a big organization, to make sure that Lilly Neuroscience continued to be very productive, and to try to put new molecules into the clinic. We were very successful at doing that. It was a very productive period in my life. In the gene expression study, we tried to understand whether one can use gene expression to identify new targets for the treatment of psychiatric disorders. We would treat monkeys with phencyclidine chronically, which is supposed to be a good model for schizophrenia, or treat them with amphetamine, which produces psychosis, and then we looked at how gene expression was changed. We were interested to see whether we could use early gene expression as targets to identify new treatments of schizophrenia. It turns out that the answer is no. The difficulty is that there are so many changes as a result of these treatments and these vary by brain region. Gene expression may go up in the frontal cortex and down in the amygdala. What are you supposed to do with that information?

TB: When we worked with phencyclidine, in the late 1950s, we found that in different doses it also induced different psychopathologies in patients with different diagnoses.

HF: You can't deal with that. And even a place like Lilly, with all the resources you couldn't run proper dose response studies in that situation. Nevertheless, we had to do those studies to decide whether our approach was useful or not. The conclusion I reached was that it wasn't a useful approach for identifying suitable drugs for the treatment of schizophrenia. Some people probably are still doing the kind of work we did, but I don't see it as being particularly useful for identifying new targets in the brain for treatment. Most of my work at Lilly was to try to manage a big portfolio and recruit new talent. Olanzapine (Zyprexa) was discovered in Lilly's facility at

Earl Wood, in the United Kingdom. They were very proud of that but what I inherited was a group who had been sitting on their laurels for 15 years, saying don't forget we discovered olanzapine. That was OK for a while, but sooner or later, I had to get that organization to be more productive. So I changed the leadership and brought in new people; now it's a very good organization.

TB: So, olanzapine was discovered before you joined Lilly?

HF: It was discovered back in the mid 1980s.

TB: Structurally where did olanzapine come from?

HF: Olanzapine is a derivative of clozapine. It's a very similar structure. The advantage is that pharmacologically it's much more potent than clozapine, so you can give much lower doses.

And because of the much lower doses, you don't get agranulocytosis.

TB: It's a great advantage.

HF: Oh, absolutely.

TB: So the starting point was clozapine?

HF: Clozapine was the starting point for olanzapine. I think what they were asking, at the time it was developed, was whether they could change the molecule in some minor way to maintain the therapeutic profile of clozapine, without risking agranulocytosis. Lilly was successful with doing that and the rest is history. Zyprexa will probably sell four billion dollars this year.

TB: A very successful drug.

HF: Right.

TB: In your new job, your task will be to set up and organize a new institute. Looking back at your career, it was a kind of step aside to become acting chair of a department of psychiatry.

HF: Why did I accept the acting chair?

TB: Yes.

HF: Probably because there wasn't anybody more qualified to do it. The Department of Psychiatry at Vancouver was not a strong department. The Division of Neurological Sciences, within that department, was very strong and had people like Pat and Edie McGeer, Juhn Wada, and Judah Quastel, very strong basic scientists.

TB: I hadn't realized you had Judah Quastel.

HF: Judah Quastel had retired from McGill when he came to UBC, but he was one of those people who had no intention of slowing down, just because he reached retirement age, and he continued to do some very good work in Vancouver.

TB: With hindsight, do you think you were successful as acting chair in a clinical department?

HF: I think I was; everybody was pleased with the administrative work I did there. It was one of these rare cases when a non-physician ends up being head of a clinical department.

TB: Actually, there were several heads of psychiatry departments in Canada who were not psychiatrists.

HF: One of them is Glen Baker, who is head of the department in Edmonton.

TB: It seems that most of the non-psychiatrist heads do just as well, if not better than, the psychiatrists. Do you think you had an impact on transforming the profile of the department of psychiatry?

HF: I think I did. I clearly turned the department more biological. But I think the whole field was going through a movement towards more biology. It wasn't anything I was doing out of the ordinary, but we did recruit, during my tenure, some very good psychiatric researchers. Probably the best of them was Peter Little, a superb clinical investigator in schizophrenia. He left, unfortunately, and went back to England. We recruited some good people there during my tenure.

TB: Did you also recruit some good people to Eli Lilly?

HF: I recruited some wonderful people to Lilly.

TB: Would you like to name some of them?

HF: We recruited Ian Reagan, who headed up the new Earl Wood site. We recruited Beth Hoffman, who is an outstanding molecular biologist. We recruited Calpana Merchant, just at the end of my tenure from Pharmacia. She's a terrific scientist. We also recruited George Nomikos, who has done some great microdialysis work, and Yang, a very gifted electrophysiologist. Both, Nomikos and Yang worked with me in Vancouver.

TB: You obviously trained a lot of people. Would you like to mention a few?

HF: I had many, many graduate students. I'm worried about doing this, because I'm afraid I will miss some of them. I think I have already mentioned David Roberts, Jim Nagy, Bill Staines, and George Robertson. I must have had 30 or 40 graduate students or post-docs during my academic career. I paid a lot of attention trying to be a good mentor. I took the task of training graduate

students or post-docs very seriously. And I think, in the vast majority of the cases, I launched them into a good career.

TB: Did I understand you correctly that in your new position, you are expected to build a research institute?

HF: Yes.

TB: From scratch?

HF: Not from scratch. Amgen has about 50 people in its neuroscience department, and my goal is probably to build that to a group of between 200 and 300 people over the next five years.

TB: What will you expect them to do?

HF: They will discover breakthrough therapeutics.

TB: Clinically, more selective and effective drugs?

HF: That's the challenge. What I want to try to do is something different than what most pharma companies do. The sad fact is that the current business model the pharmaceutical industry uses is not viable. Companies cannot discover and develop drugs quickly enough to meet the goals that investors expect. If you want to grow the value of your company by 15% a year, which is what Wall Street would like to see, nobody is able to discover and develop drugs, quickly enough to meet that target. As we speak, Bristol-Meyers is in huge trouble, Merck is on its knees, Schering, I don't know what they're going to do, they're in terrible shape. Among all of them, I would say Lilly, right now, probably has the best pipeline.

TB: So, Lilly is OK?

HF: But also, Lilly has got a huge problem starting in 2010 because in 2011, it will lose Zyprexa, a loss of between four and six billion dollars a year. That's the expectation. And Lilly, right now, hasn't the ability to make up for that loss in terms of new innovative products. And this is true across the industry. R&D and other expenses have been going up and productivity, in terms of new launched molecules, is going down. The investment is not producing what we had hoped. There are many reasons for that. It's a very complex issue. The bottom line is that the current business model is not viable. What I'm working very hard on right now, is to try to think about how we can create a new model, how to come up with new approaches to developing novel therapeutics for important human diseases that will sustain the growth companies need. It's a very, very complex question and I don't have all the answers.

TB: Would the field of psychotropics that had clinical end-points with better predictive validity help?

HF: It would help. I believe society is willing to pay for true innovation. And I think they are willing to pay for a medication that you can say, in advance, is going to work for the patient. So the dream for the future is the genotype. You determine, on the basis of the genotype, that there is a very high probability the medication will work, or will not work, for this particular patient. So don't waste time and money giving the drug to somebody for whom it is not going to be effective. We have seen the first example of that in the treatment of breast cancer. That's the future. And society, I think, will be more than happy to pay for those kinds of advances. But it requires a combination of diagnostics and therapeutics, and most companies are not doing that.

TB: Do you think genotyping will be the answer?

HF: I'd be in a much better position to answer that question a year from now, because I am working through these kinds of questions. And what I have to decide is where Amgen neuroscience is going to place its bets. We will certainly do some work in neuropsychiatry.

TB: Glad to hear that.

HF: But I think one of the good things about this meeting, is that I'm starting to see some changes I've been advocating for a long time. There is more and more discussion today about how schizophrenia is not a useful concept for research. It's too vague. The way that DSM describes schizophrenia, as somebody pointed out at this meeting, is that you can have two patients with schizophrenia who essentially don't share any symptoms. That may be OK for clinical practice because it doesn't make any difference. We don't have any differential treatments right now anyway. Remember the old story about schizophrenia being the graveyard of neuropathology. Schizophrenia will be the graveyard of molecular biology. It will be the graveyard of imaging. It will be the graveyard of any technology that you try to apply to it, because it is simply too diffuse a concept to be useful for research and development purposes. Now, what is happening at this meeting, which is very encouraging, is that people are starting to take this idea of endophenotypes seriously. So let's focus on the cognition of schizophrenia.

Let's focus on positive symptoms of schizophrenia. The biology of those things, are going to be different, and therefore, the medications are going to be different. It's interesting that the pharmaceutical industry is still trying to kind of grapple with this. There is the mantra over the last

few years that we need to develop very potent, very selective compounds, and these compounds will be a good treatment for depression, for example. I don't think that's going to be true. I think it might be that very potent, very selective compounds might be good for treating one aspect of this thing we call depression, but not the whole thing. And maybe the reason that SSRIs have been so successful is that there is only one target for SSRIs, the serotonin transporter. But, remember, there are 17 serotonin receptors whose activity is being impacted by that SSRI. So, in fact, an SSRI, is a very "dirty" drug because its immediate post-synaptic consequences are mediated by at least 17 receptors that we know about.

TB: Now, before closing, is there anything else you would like to add?

HF: No.

TB: I have one more question. Could say something about the ACNP? When did you become a member?

HF: I joined ACNP very early in my career. I felt very privileged to get into the ACNP. I think I must have been one of the very few Canadians who were accepted for membership, and I think I was accepted in 1976, 18 years ago. And I think I have attended just about every meeting since then. Without question, if I could only go to one meeting every year, it would be the annual meeting of the ACNP. I had the privilege of serving as the journal editor for *Neuropsychopharmacology* for a few years. Unfortunately, I had to give that up when I joined industry. But I enjoyed doing that very much, and I was honored to contribute in that way. And I've been on Council for the last three years. Today, in fact, is my last Council meeting. And that's been a lot of fun too. So, I felt very close to the College and I've, without exception, enjoyed my interactions.

TB: Just one additional question; what would you like to see happen in the neurosciences in the future?

HF: Probably exactly what we just talked about a minute ago. Let's get rid of these useless concepts or syndromes, useless for research purposes. Let's start focusing on endophenotypes.

Hopefully, we'll have better luck there. Let's start treating patients for their specific symptoms, so maybe this kind of medication for psychosis, this kind of medication for cognition, a different kind of medication for negative symptoms, etc. If we can genotype patients, so the physician can be helped in understanding what will be in the best interest of his patient, that would be a wonderful step forward.

TB: Well, on this note we should conclude this interview. Thank you very much.

HF: It's a pleasure. Thank you.

18. ALFRED M. FREEDMAN

TB: This is an interview with Dr. Alfred Freedman²⁰ for the Archives of the American College of Neuropsychopharmacology. We are in the apartment of Dr. Freedman in New York. It is November 3, 2000. I am Thomas Ban. Let us start from the very beginning. If you could tell us when and where were you born and say something about your education and early interests?

AF: I was born in Albany, New York, a small town at that time, although it was the capital of New York State. I was born on January 7, 1917. That sort of appalls me when I realize soon I will have my 84th birthday. My parents were immigrants from Eastern Europe. My mother was born in a small town, near Vilnius; that we always called Vilna. The small town she was born in, we called Smargon, although the name on the current maps is Smargoni, which is actually in Belarus at the present time. Anyway, she came here when she was about eighteen or nineteen years old, in the early twentieth century. My father was born in Poland in a small town, Wisocki Modiuwetz. He studied to be a Rabbi in a city, Lomza. My Polish colleagues would tell me, it's pronounced "Womza." He came here around the same time as my mother, and they met and got married. They lived and had small businesses in Massachusetts, which did not succeed. So finally they ended up in Albany, running a small grocery store. I was the third child. I had two older sisters and we lived above the grocery store. We lived in an, I would say, rather poor mostly Irish and Polish immigrant neighborhood, where I picked up a few words of Polish that I still remember. Anyway, I attended public school in Albany. Right next door to the school was the public library and that was heaven for me. Every Friday, they used to have a storytelling hour, which I attended. After that hour I would get a lot of books to read for the next week, and that was a very happy occasion. That was my life until I was ten years old. I did very well in school. As a matter of fact, I entered a citywide

²⁰ Alfred M. Freedman was born in Albany, New York, in 1917. He earned an undergraduate degree at Cornell University, in 1937, and then studied medicine at the University of Minnesota, graduating in 1941. Freedman trained on the children's service of Bellevue Hospital in New York City, staying on as a staff psychiatrist, from 1948 to 1955. After working in several different pediatric posts, he became chairman of psychiatry at New York Medical College in 1960, from which post he retired in 1989. Freedman died in 2011. He was interviewed in New York, New York on November 3, 2000.

achievement test when I was in the 5th grade and received the highest grade in the city! By that time my father had been doing very well in real estate investments and, so, we moved from the south end of Albany, which was really the poorest part of the city, up to Pine Hills, which was one of the posh neighborhoods. And there I finished the 7th grade. After that I went to the junior high school, which was some distance away.

Unfortunately, when I went to junior high school in the fall of 1929, my father's investments all went bad and he lost quite heavily. So, actually, he again opened up a grocery store, not far from our home on Pine Avenue. It was very hard times. He had to work very hard. My mother also worked in the store and it was very difficult. I was in high school but I spent all available time helping out in the grocery store. My greatest interest was in mathematics and science. When I graduated, I got a medal for my achievements in mathematics and science. I liked, particularly, chemistry. I remember it as my very favorite subject. The mathematics I had at high school was limited. We did have advanced algebra, but I remember very well our poor teacher. It was really a bit beyond her what she had to teach, but we used to help her out by making suggestions. She was very grateful for that. I was amazed when I got to college and found all those bright kids from New York City, who had studied calculus in high school. It was the Great Depression when I went to high school and we had a very marginal sort of life in those years. I remember that I started driving the truck for the store when I was fourteen years old and was picked up once by the police. Fortunately, in my father's good times, he became very friendly with one of the superintendents in one of his buildings, who became a policeman. So, he, fortunately, got me off. I remember, in those years, driving down hurriedly to the bank, to make a deposit before the bank closed at 2:00 o'clock, in order to meet the deadline of the checks my father had written to pay the bills that he couldn't delay anymore. So, it was a difficult time. I used to work in the store after school, as well as on Saturdays. On Sunday, we kept open the store for a half a day and I would run that myself to give my father and mother a little time off. In addition to the grocery and meat market, we got the idea of having newspapers and magazines in the store, which my parents allotted to me to handle. All the money that came in from the papers and magazines was put aside for me to go to college. In the meantime, one of my sisters had started in college at Cornell. My parents worked very hard to make sure that there was enough money for her to finish college.

TB: There were three of you, right?

AF: There were four of us. I also had a younger brother, five years younger than me. There was actually another boy in between the two of us, who died when he was six months old.

TB: Both of your older sisters went to college?

AF: All four of us. My mother was unceasing in her efforts. She wanted us not only to go to college but become doctors or lawyers. For the girls, graduate school would have been fine, for her. Anyway, I realized very soon that as far as college was concerned, in Albany, there was a Normal School for teachers that later became a college and is now the basis of the State University of New York in Albany. It used to be right next door to the high school, but later on, it moved away from there. So, that was always a possibility for me if I wouldn't win a scholarship to go to Cornell. They had statewide scholarships in those years that were distributed by county. Albany County had three, and I won one of those three. Then I won an additional state tuition scholarship that with the other scholarship was the basis of my going to an Ivy League College. There were several things, I might say, that shaped my development in high school. One was my devotion to chemistry and physics. Also, there were two books that were very important to me. One was *Arrowsmith* by Sinclair Lewis that introduced me to the whole idea of devoting one's life to research. I remember the experiments he was doing on bacteria and his research in the Caribbean. That book had a great impact on me. The other one was Paul de Kruif's *Microbe Hunters* that described the life of those who made important contributions to the progress of bacteriology and the elucidation of the cause and cure of disease. They were Koch, Pasteur, Walter Reed and many others. After reading that book, I wanted to become a researcher.

TB: Did any of your teachers have a major impact on deciding on your career choice?

AF: I think the teacher who seemed most interested and encouraging, was my history teacher. Her name was Ms. Bradt. They were all friendly, I got top grades, but I never got any particular encouragement. And I remember that we had a man who taught us chemistry. His name was Job, Mr. Job. He was a rather aloof man but a good teacher. As long as you did your work that was okay. But he wasn't a person to say, "Oh, that's very good, what are your plans, you might think of studying biochemistry." No, there was nothing like that. I didn't have any of my teachers give me encouragement. It all came from me.

TB: So it was your decision entirely without any encouragement?

AF: Well, as I said, my mother was very enthusiastic to have me and my brother become doctors, and my father joined her in that. He was busy in the store all day and when he came home, he had a bite to eat and would fall asleep at the table. So he didn't say very much in that regard until I had become successful and, then, he wrote to me, "You did it all on your own."

Anyway, my sister graduated from Cornell in 1933, and I graduated from high school in the same year. And, of course, that was a very important year, not only because of my graduation, but also because of my perturbation in regard to going to college and about my future life. And, as you know, that was also the year Hitler came to power.

TB: Yes, in the spring of 1933.

AF: To go back a little in time, we were all very impressed in 1928, when Franklin Delano Roosevelt became Governor of New York. He was very popular and impressive, though my father said they elected a cripple as a governor and had to install elevators in the executive mansion to accommodate him. But Roosevelt was truly a charismatic figure. He always drove around in an open car in Albany; he'd sit in the back and a chauffeur in the front. And I remember standing on the main street one day when they were driving along. People started clapping and saying hurrah. Men took off their hats and waved them. He had a cigarette in a cigarette holder and tipped his hat. I had followed the election in 1928, when Al Smith ran against Herbert Hoover. We had listened on the radio to the Democratic Convention, in 1932. It was quite a battle between Roosevelt and Al Smith; he was bitter because he looked upon Roosevelt as his protégé. It was Smith who persuaded Roosevelt to become Governor. Anyway, eventually Roosevelt became President and that was important for me because of the various programs he introduced to do something about the depression. And then Hitler came into power. It was very troublesome. He was a threat to the world, but particularly to us Jews. I was studying at Cornell but my funds were very inadequate. My parents had some money that they gave me, but I depended mostly on my two scholarships. As a result of Roosevelt's efforts, they formed what was called the National Youth Administration (NYA) that gave money for young people to get jobs. So I got a job cleaning the aquaria in a research laboratory under a man named Myron Gordon. I was 16 years old when I went to college and being from a small town and a family that was, in many ways, out of the mainstream, I was very poorly prepared for college. I really felt very lost. At times, during my first

year, I felt like giving it up and going home. It was a feeling of being a burden on my family; they had difficulty making out anyway. But, in any event, I persevered.

TB: So you worked in an aquarium while in college?

AF: Yes. But sometimes during the first year, my job in the aquarium was changed from cleaner to becoming a translator. What actually happened was that one day Myron was sort of groaning over some stuff, and he asked me whether I knew German. When I told him that I did, since I had German in high school, he opened a scientific journal, pointed to a word and asked, “Do you know what this is”? I did. Soon after that incident he said, “Forget about cleaning the aquarium; you can translate German for me. Here, take this home. I want you to translate this article and this will be your job here.” This was very nice, because I was able to work at home instead of going at night to the aquarium. He gave me a dictionary and I would translate the articles he had. Myron Gordon’s research was essentially on the genetics of melanoma. He found that by crossing two breeds of fish, *Xiphophorus Hüllera*, a sword-tailed fish, and *Platyopocilus Maculatus*, a tropical fish, one of the hybrids got black spots that would develop into melanomas. I found all this fascinating. I became taken up with this, because the articles were about melanomas, crossbreeding fish, and genetics; the material was scientifically stimulating. I was avidly reading the books Myron Gordon had in his library. One of the classics of the time on the topic was Ewing’s *Neoplastic Disease* and I used to read on melanoma and other stuff in it. I was really taken by the topic, and more or less decided that if I go to medical school, I’m going to work on cancer and I’m going to find a cure for it. Then, one day, I remember him talking to me about his correspondence with a man who had been doing similar work in Germany, and saying, “Imagine in a letter I got in 1934 or ’36 from this man in Germany; he closed his letter instead of ‘best regards,’ by writing ‘Heil Hitler.’”

TB: What did you major in?

AF: It was a pre-med major. But I was determined that I was going to complete a major in mathematics, physics and chemistry. I took calculus in my first year and I did very well in it, as I recall, and became very interested. During my first year, I didn’t get involved in any extracurricular activities; I was busy translating and with my studies. But they had a series of lectures every year by some distinguished person and I attended those. There was a lecture I particularly remember, given by Eddington, a very famous astronomer, cosmologist and scientific philosopher. He talked about atoms and atomic energy, and that opened a new world to me. I ended up getting a flat 100

in my freshman chemistry, that was quite spectacular, and I got very high grades throughout that year from all the different subjects. But I decided that medicine was not for me; I wanted to study physics and become what we called in those days, an atomic scientist. So, when I went home and told my parents that I was going to give up medicine and was going to become an atomic physicist, they were dismayed. And I remember my father telling me that for thousands of years the men in our family had been Rabbis or teachers and he was the first one who did not finish his rabbinical studies and became a businessman because his father, my grandfather, a Hebrew teacher, moved to the United States. He didn't have much appreciation for me becoming a professor of physics, and my mother felt kind of bad about it also. Anyway, by the end of the summer, I decided to go back to my original plan and study medicine.

TB: So you went back and continued with your pre-med courses.

AF: One always wonders what would have happened if one had done it in the other way, if I would have become an atomic physicist. It was 1934, just the early days that the new field was opening up. It would probably have been very interesting too, because the following year Hans Bethe, a famous physicist, came to Cornell after leaving Germany, and organized a whole unit of Nuclear Physics. Later on he moved to Los Alamos and was involved in making the atomic bomb. So I might have been involved in making the atomic bomb.

TB: But you decided to prepare for medical school.

AF: Yes, and it was tough going. But I succeeded and had even some fun. I can't look back and say, "Oh, those wonderful college days." It was stressful with a lot of tension. I was also concerned about how my parents were making out. They had many crises in their business, and when I got those checks for my scholarship, I foolishly endorsed them and sent them home. My father was furious and sent them back. But what I did indicated my own anxieties in regard to the home situation.

TB: Did you continue doing well at school?

AF: I did well in school, as you might expect. I had some problems so with some courses, like comparative anatomy. I think I only got a B in it, but I had A's in chemistry, physics, and all the other subjects. I had to take Freshman English and it turned out, Professor French, the man, who was teaching it and who was my advisor, had been somebody my sister knew. He was a very nice person. I enjoyed his course and I did very well. Actually, I took also second year English that was

not required. He was very encouraging and invited me once to his home for dinner. He liked the essays I wrote, particularly when I just wrote of my own experiences or life, rather than trying to be another Shakespeare or Hemingway. So he was a very important person in my life. He encouraged me to do things I could do. I actually did complete a major in chemistry and in physics. I had to take sort of a short course in biochemistry, but I took the regular course and also took physical chemistry that was not required, and instead of taking the short course in physics, I took two years of physics. The physics teacher was very impressed; he was very good to me and encouraged me in my activities. I must say, in retrospect, I had social phobia. I was very timid and very shy. I found it very difficult and it would not occur to me to ask anybody to do something for me. A third person, who became very important for me, was a doctor that I met. Actually, this was the period of time when the civil war broke out in Spain. I was very taken up with the Spanish civil war and was desperately eager for the Loyalists to hold out against Franco. And there were on the campus various things going on, which I entered in supporting the Loyalists. And, through this connection, I met this couple. One was a doctor. He was the head of pathology at a center for tubercular patients. He was born in Germany and had been in the army as a doctor in World War I. Then, by 1922 or so, he decided to go to the United States. His name was Max Pinner. So, when I was introduced to Max Pinner and he said to me that he was a pathologist, I said, "Oh, that's interesting. I've been doing reading on cancer." He said, "Oh, really. What have you been reading?" I said, "I've been reading Ewing's textbook on cancer." And he said, "Oh, what are you interested in?" So, I started telling him about melanoma and he became very interested and friendly. Actually, they had me to their house and I saw a lot of them. Then, in the fourth year, it was time to apply to medical school. And, as I said before, I had a bit of social phobia. Anyway, I was very timid. It didn't occur to me to go to Professor French, or to the professor of physics, or to Max Pinner and say, "I'm worried about getting in medical school." I just could not go and tell them, "You know I'm Jewish; I have no big connections; my father and my uncle are not doctors; can you advise me?" Instead of asking for their help, I just went and handed in my application. But in spite of my high marks, Cornell turned me down, and so did all the other medical schools I applied to.

TB: Did all schools turned you down?

AF: I only applied to schools in the east and I remember being interviewed at the New York Medical College and they looked at me and said, "Boy, look at these grades. Did you ever see anything like that?" They turned me down, though, because, you know, I was Jewish. One of my Jewish classmates whose uncle was a doctor on the staff there was accepted. You had to have connections in those years. I had none. And I had hoped to get into Albany Medical School, but there again, I had no connections, and they gave me a hard time. My father and my mother were immigrants, so they were not impressed. I recall going to the University of Rochester and being interviewed by Dean Whipple, who was a very famous surgeon. He was very nasty and asked, "Why do all you people want to become doctors? Why don't you just work in the grocery store like your father does?" Anyway, that was a terrible blow. I didn't have money to travel back and forth, so I hitchhiked to Rochester, and I remember while standing at a crossroad while hitchhiking back to Ithaca, of thinking the hell with all this, I should just leave and go Southwest and see what will happen.

TB: What did you do?

AF: In January 1937, I enrolled in the graduate school in Zoology, in the department that Myron Gordon was in, and I began my first research project there. In my readings on cancer, I had been really impressed that there were certain substances that caused cancer, so I thought I should try to see what would happen with the development of cells if I raise them in a solution of carcinogenic substances. I had taken a course in experimental embryology and learned about various embryology organizers. I was also familiar with the writing of a German named, Holtfreter, on this subject. So, I went out with the help of some of the others and we collected the eggs of early spring frogs. And then, I got some cancer producing substances and raised the eggs in a solution of these substances. Meanwhile, someone told me about the possibility of getting admitted to medical school at University of Minnesota. So, I applied and to my surprise I was accepted. All I had to do was take a pre-med examination. One of the women instructors in the laboratory carried on my work and when the eggs were hatched into tadpoles, she actually made sections of them and sent them to me in Minnesota. But, before I left I went to say good-bye to French, and when I told him the problems I had, he was furious with me and said, "Why didn't you tell me your problems? Why didn't you ask me for advice? I'd written a letter for you." If I had told him, he would have gone over to see the dean of the Medical School of Cornell in Ithaca, one of the two

schools they had at that time, and could have saved the problem. Apparently, he was an advisor there with a lot influence. The same thing happened when I went to see Max Pinner. He also said that he could have helped me to get accepted at New York University. It was the first time in my life in which I found myself unable to advance myself by asking for things. It happened again many times later in my life. So many of the things in my life I achieved passively. Anyway, that was the end of my Cornell experience.

TB: And you left for Minnesota.

AF: Well, it was a long, long trip. I remember going out there by train. I had never been west of Rochester before. So that was a whole new world and I did not know what to expect. I arrived there in the evening and I spent the night there in a hotel close by to the railroad station. And then, I went up to the campus the next day and looked for a place to stay. At Cornell, the dormitories were too expensive for my very limited budget. But by the time I went to Minnesota, the situation, thanks to Roosevelt, was somewhat better. Of course, medical school in Minnesota was a big bargain compared to New York. It was free for residents from Minnesota, and also from North and South Dakota and Montana because they had no medical school. And it was about \$300.00 for others. I also found a cheap place to live, right around the campus. It wasn't too bad. Compared to Ithaca, prices were very reasonable at that time in Minnesota. We were still in years when there was a so-called numerus clausus for Jewish students. They would decide in advance how many they would take every year. As I discovered later, there were three of us out of state Jewish students in my class. The other two were from New York City. One had gone to Brooklyn College and the other, I think to City College. It turned out that the dean of the medical school was a very liberal man, who was troubled by the quota for Jewish students.

Contrary to my years in college, where I excelled in school, in Minnesota I didn't devote myself to my studies in the first two years. I think, in some a way, it was a sort of reaction to that I didn't get into Cornell, or Yale or Harvard. I wasn't industrious in doing my work and neglected my studies, so I got B's. It went to the extent that instead of taking Part I of the National Board Examinations at the end of the second year, I did it sometime in the third year. To my surprise, it turned out that I got the highest grade in biochemistry for the country. I can't explain how it happened, but it turned out that way. I did various things during those two years; as if I was trying to make up for all that I missed as an undergraduate. So, even if I had to miss a class, I went to the

weekly concerts held for the students by the Minneapolis Symphony Orchestra and became a devoted follower of Dimitri Metropolis, its conductor. It was the time when the Spanish Civil War was winding up. It was also the time of the Munich Agreement and the onslaught on Czechoslovakia. I remember being very involved in those issues and going around the city in a car with a loudspeaker shouting, "Protect Czechoslovakia against the Nazis." And the group that I was involved in, organized a big rally on the steps of the big auditorium of the University. Unfortunately, it was the day after Chamberlain went to Munich and announced that there's going to be peace; that Hitler would have Czechoslovakia, or the Sudetenland. And I remember the professor of history got up and said, "Well, Ancient Bohemia will not die." It was very sad.

TB: So you got involved more in politics than in your studies.

AF: I liked histology in the 1st year, and in 2nd year, pathology really turned me on. And I did very well in it. It was very funny. The other students thought I was sort of unusual, but on the other hand, I was sort of a recognized expert on politics and international events. When sitting around at lunch, one or another would ask, "What do you think is going to happen with Hitler?" or "Is he going to take the rest of Czechoslovakia?" or things like that they had heard but had not read very much about. So anyway, that was sort of interesting.

TB: What about in the 3rd year and later on?

AF: In the third year, I was really taken with clinical work and became enthusiastic about my studies. So, in the last two years, I did well, but I never made up for what I missed in the first two years. I also met an associate professor of physiology, in charge of neurophysiology, through some mutual friends, and told him that I wanted to devote my life to research. So he said, "Well, why don't you come up and maybe we can work out a project." He was doing research in traumatic or neurogenic shock, and being a neurophysiologist, he was interested in what role the nerves played in it. At that time, the prevailing authority in traumatic shock was Professor Blalock at Johns Hopkins. He thought that the big danger was the pooling away of blood from the various parts of the body, that blood pressure goes down, and not even blood transfusion could help in preventing death. And this associate professor I worked with had the idea that we do a project. We bound one leg of a cat tight so that there could be no accumulation of blood in that leg. And then I was hitting the leg of the cat with an iron pipe, so that the cat would go into shock, its blood pressure dropped, and eventually it would die. And then, by doing an autopsy, we established that the accumulation

of blood in the traumatic area was not different in one leg from the other, and concluded that in the pathological mechanism of traumatic shock, pooling away of blood never plays an important role. I actually had my first paper on our findings in this research. I think it was published in the *Journal of Physiology*. Then, we did another paper together that was published in the *Proceedings of the Society of Experimental Biology*. And on the basis of these two papers, I was elected as an undergraduate to the research society Sigma Xi, which was a big honor. Very few students got elected to that prestigious national organization. I remember that at the dinner in honor of the new members, Bell, the Professor of Pathology, was the principal speaker. The main point of his speech was, "Well, what you have to do as a researcher, define your area very early, and just stick to that for life. For example, I became interested in the pathology of the kidney, so I devoted my life to glomerular nephritis, nephrosis, and all kinds of things with the kidney." I thought to myself that's not for me. I'm going to be another Leonardo da Vinci.

TB: So you worked in neurophysiology while in medical school?

AF: That's right. And, the guy I was working with was Herman Kabat, who had his PhD in Neuroanatomy and Neurophysiology from Northwestern. I used to work with him on his experiments. He was interested in the anoxia of the brain and the experiments of closing off the carotids, for a short time, to see which cells were more sensitive to the lack of oxygen. He had a collaborator, a professor of neuropathology, whose name was Baker. At the time, Psychiatry was a subdivision of the department of medicine, and Baker was assigned the task of teaching psychiatry. It was a very uninspiring teaching of Psychiatry. He handed out notes to read, it was a kind of one, two, three. If you had asked me the subject I would least likely want to pursue as a career at that time, I would have said Psychiatry.

TB: Could you tell us something about those notes?

AF: We got a list of symptoms for diagnosing schizophrenia and manic-depressive psychosis. He was sort of more interested in showing us possible pathology than talking about clinical symptoms. The one thing I remember in psychiatry was a psychiatrist in town who was in private practice. He was one of the originators of ECT, and he was experimenting with it. We went to his office for a demonstration. I remember he had all kinds of equipment and batteries. I think that was the most interesting lesson we had in our course in psychiatry.

TB: What about your clerkship?

AF: We had rather staggered clerkships. We were divided in four groups and I was in one where we worked all summer, and, then, I had the fall off, and I went home. Before leaving, Kabat, the guy I was working with in neurophysiology, told me that while I'm in Albany I should visit Harold Himwich, the Professor of Physiology at the Albany Medical College, who is working on the same sort of things on the brain as he was.

TB: Could you just remind us what you were working on with him?

AF: I was working with him on anoxia of the brain, and its consequences on brain function. So when I was in Albany, I went down to the Albany Medical School and met Harold Himwich. Do you know him?

TB: Yes. I did know him.

AF: Well, Himwich was a bossy but friendly guy and when we met he said, "Yeah, I read your rotten paper." And then he invited me to spend some time in his lab before returning to Minnesota. He had an assistant at that time whose name was Fazekas, also a medical student, who later became Chief of Medicine at the City Hospital in Washington. I spent some time working with Harold on his projects. In those days, the belief and the conviction was that all metabolism of the brain was due to glucose. And he was working on that, not only in adult but also in fetal brains. Since the metabolism of the brain was at a lower level in the brains of the fetus and the newborn, in case of anoxia, a fetus, or a newborn cat, could survive longer than an older one, and would have less damage to its brain. Anyway, I worked on those experiments with him and Fazekas.

TB: For how long did you work with him?

AF: Just during my vacation in 1940. I had to go back to school and finish my studies. I enjoyed working with Harold Himwich, and the time I spent with Fazekas and a couple of the other people in the laboratory. Albany had a large Little Italy, and we used to drive there to some typical Italian restaurants with checkered tablecloths to have spaghetti and meatballs. It was a very pleasant time for me, I learned a lot from Harold Himwich, and the work he did was useful to the research I did with Kabat on traumatic shock and its possible prevention. Then just before my return to Minnesota, I got a telegram from Kabat that took me a little while to comprehend. It said: "Adrian in oil, please come right away." And then I realized that he was talking about adrenaline in oil that he wanted me to work on. It was in late 1940, when everything was tuning up for war. Research in traumatic shock, and especially, in its possible prevention, became of special importance and

Kabat thought that if we could show that brain anoxia, traumatic shock, could be prevented by the administration of adrenaline in oil, the army would love it.

TB: So you went back to Minnesota after your vacation and continued your research with him?

AF: Yes, I did. We published a paper on our findings. Adrenaline in oil really did not work very well. In the meanwhile, I was finishing up my clerkship and headed for graduation. Minnesota was a very friendly place. I made a lot of friends and many times I've regretted not staying there, because I made good contacts with the clinical people. But, I think, with the war impending, I wanted to go back east and be with my parents.

TB: Where did you do your internship?

AF: I thought I'd like to go to New York to do my internship, and, Max Pinner, who, by then was Chief of the tuberculosis service at Montefiore Hospital, was ready to arrange for me an internship in his hospital. But I decided that I wanted to get a big city experience. So I became an intern at Harlem Hospital.

TB: Is there anything else you would like to tell us about your experiences in Minnesota?

AF: Yes. Prior to starting with my internship, I had still to complete my clerkship in obstetrics at the City Hospital in Minneapolis. I had never delivered a baby before, but on the day, soon after my arrival to work, the resident I was assigned to, left me to have his supper. As soon as he went down on one elevator, another elevator came up with a woman yelling and screaming – she was about to deliver a baby. Fortunately I had a very good nurse there with me, but by the time she got me into my gowns and gloves, the baby's head was already beginning to appear. She stood over my shoulder and kept on telling me what to do and how to take hold of the baby. Then I brought the baby out, tied the cord, and under her supervision, cleaned the baby's throat. That was a big moment. It was the first baby I ever delivered. I delivered a lot more after that. Anyway, it all went well. Then, when the resident returned from lunch, he told me the big news that Germany had invaded Russia.

TB: What year did you graduate?

AF: In June 1941, and I started my internship on the 1st of July.

TB: So you moved, in June 1941, from Minneapolis to New York?

AF: Yes, but I went to Albany to spend a few days with my family before starting with my internship in New York.

TB: Could you say something about your internship?

AF: It was a very busy internship. We got very little teaching. I think it was a poor choice on my part, but in any event, I spent the year with a very friendly bunch of people. My zeal for research did not leave me and Harold Himwich told me that a friend of his, with the name of Bullova, was doing research at Harlem Hospital. Those were the days when all through the country, they had stations that had various types of antisera for pneumonia, and if someone had pneumonia, they typed it to provide the most appropriate treatment. And Bullova dedicated his life to develop antisera for pneumonia. His ward was completely oxygenated, with signs around, don't smoke and don't light a match, because the place could blow up. He had an associate who was a refugee from Europe, who was doing some research that dealt with nucleoproteins. I told them about my interest in research shortly after I started to work with them. As you know, by that time Hitler had already taken over Czechoslovakia, and invaded Poland. So, for a few months, I attended my duties at the hospital and was doing my research with Bullova. Our hospital used to send an ambulance to the Polo Grounds, where the Giants football team played, and all of us interns who were interested in football went with the ambulance to watch the games. And, then, I vividly remember that on December 7, 1941, while sitting and watching the game, I suddenly realized that something extraordinary was going on. It started with an announcement, as I recall, asking Col. Donovan to call the operator. Then, about 15 minutes later, there was another announcement asking Col. Donovan's chauffeur to go to gate 21. While the game continued, some people were paged, but I only found out overhearing the radios on the street, while returning to the hospital, that the Japanese had bombed Pearl Harbor. Although I signed up for a two-year internship, I told the hospital that I was leaving after my first year. It was okay because I needed only a one-year internship to get my license. In the meantime, I talked to Harold Himwich, who had some contacts with the air surgeons.

TB: So, you left to become an air surgeon?

AF: Foolishly, I didn't look into what it would require to become an air surgeon. Apparently, I didn't qualify because my eyesight was poor. So, I ended up in the Army Air Force, as it was called then. But I was just assigned as a regular doctor, and I would have done better if I had continued with my training and had some special skills. I worked in a dispensary and escorted troop trains as

medical officer. And on one of those trains, coming back from Colorado Springs to Illinois, I met Marcia. We became attracted to each other and six months later we got married.

Before we got married, I was sent to get further training in the army at Carlisle Barracks in Pennsylvania. Most of the medical officers in Miami were middle aged, and they picked me immediately as the youngest one, and who was single and had no children, to go to Carlisle. So, I spent 12 weeks marching around in the snow and studying military tactics. When I got back to Miami Beach where I was stationed, we got married. Shortly before my wedding, I was asked by our commanding officer if I'd be interested in going to a laboratory school at Johns Hopkins. I grabbed at the opportunity, because I realized that I would be stuck by remaining just an ordinary doctor. So we went to Baltimore, and after 90 days, I returned from Baltimore to Miami as a laboratory officer. In the meantime, Arthur Mirsky was made the Chief of the laboratory. So, when I came back, I got a job in the laboratory in one of the hospitals. I was running the hematology service. As soon as I began with my new activities, I started to look for a research project. And, I recall, that I read in *JAMA* a paper on heterophile antibody in viral pneumonia that was quite prevalent then, particularly in the army. So I decided, well I'll study heterophile antibodies on random soldiers in the hospital and discovered that it was the antibody of infectious mononucleosis. I wrote this up with Mirsky and was going to send it to *JAMA* where I got the idea from. But Mirsky had the idea that we should send it to a military magazine because it would be better for my career. It was bad advice; the paper got buried and lost. By the time it appeared, other people got all the credit for the discovery of heterophile antibody in infectious mononucleosis. Anyway, it was my research. I was in the laboratory for about a year before I was transferred to become in charge of a laboratory in Gulfport, Massachusetts in the station hospital, which, at the time, had 1,000 beds. It was quite a big enterprise.

TB: So you moved from Miami to Gulfport.

AF: I had a fairly good size staff in Gulfport and while I was doing my job, one of our soldiers who just returned from the Pacific committed suicide by taking Seconal (secobarbital). So, I collected the gastric contents as well as some blood and sent it to the regional laboratory for analysis because we did not have the necessary facilities for that. I found out from the Surgeon General's library that there had been no reported cases of successful suicide, so far, with Seconal. I don't remember any longer whose drug Seconal was, but I remember that its advertisement said that it's a safe drug, insofar as suicide is concerned. And when I got my figures of the blood levels

of Seconal in the soldier, I called the professor of Pharmacology at Tulane University who confirmed for me that the level in the blood was high enough to cause a fatal outcome. So, I wrote this up in a paper, and this time I didn't make a mistake but sent it to *JAMA*. In my paper, I wrote that I was reporting a case of Seconal overdose with fatal outcome. I also said that there had been no reported cases of successful suicide with Seconal in the literature. Then, in the next issue of *JAMA*, a letter appeared saying that Captain Freedman surveying the medical literature was inadequate. If he had looked at the coroner's reports in Los Angeles County, he would have seen that Aimee McPherson, a famous evangelist, had committed suicide by taking Seconal a year or two before my report.

TB: So, during the time you were in Gulfport, you reported on a case of fatal overdose with Seconal.

AF: Actually, in Gulfport, I became very friendly with the psychiatrist, who was from St. Louis. So, I used to spend time with him and he would show some of his cases to me. I was spending a lot of time on the psychiatry ward there and found it quite interesting. I also remember telling him that I might go into psychiatry, eventually, to study the biochemistry of mental illness.

TB: So, is this how you got into psychiatry?

AF: I might have gone directly into psychiatry, but I thought I would get two years credit for my pathology boards, for the work I did in the army.

TB: When were you discharged from the army?

AF: I was discharged in January 1946. I was officially on leave with pay from January and actually discharged in March.

TB: What did you do after your discharge?

AF: My intention was to go into pathology, and Dr. Pinner told me that I should contact his friend, Dr. Klemperer at Mt. Sinai Hospital, who was the head of pathology there. When I met Dr. Klemperer he said, "Oh, anybody that my friend, Max Pinner, sends has a place in my laboratory." So, after a brief vacation in Florida with Marsha's parents, I reported for work at Mt. Sinai in New York. As it turned out, the place was flooded with veterans like me, and we were given work on a voluntary basis.

TB: So did you, or, didn't you have a job there?

AF: I didn't have a regular appointment; I couldn't even go and eat at the staff dining room. After going to the dining room a couple of times, they told me, and also the others, that we should not come back. So, I decided, at that point, that I'm not going to spend my life in a mortuary doing post mortems, and started to look around for a job. Harold Himwich, by that time, had left his job as professor of physiology in Albany and became director of research at Edgewood Arsenal in Maryland. And when I called him, he invited me to come down to work with him. So we moved from New York and I did research with Harold on anticholinesterases, the German nerve gases. By blocking cholinesterase, the enzyme responsible for breaking down acetylcholine, these gases left the acetylcholine unchecked in the brain that lead to death within seconds. Somewhere, along in there, I got the idea of trying to inject the DFP (diisopropyl phosphorofluoridate) into an animal to see what effect it would have. And, lo and behold, when we injected it, the cat got grand mal seizures with a spectacular EEG. Harold became very excited about that and thought that it might be the cause of epilepsy as a deficiency of cholinesterase or an excess of acetylcholine. So anyway, we did a whole series of experiments in this area of research. In the meantime, I read a paper from which I learned that there is more cholinesterase in the brain after birth and was thinking that the acquisition of intelligence in some way might be related to changes in the level of acetylcholine. While working with Himwich, I realized that I'd really prefer to work on humans rather than the cats and rabbits we were working on. It might also be a factor that several of my friends were going into psychiatry. So I thought, well, I should train also to become a psychiatrist. I actually wanted to become a child psychiatrist, and work on the biochemistry of the development of intelligence.

TB: So this was the time you decided to leave pathology for psychiatry?

AF: When I told Harold that I would like to get into psychiatry, he introduced me to Karl Bowman, who was professor of psychiatry at the University of California in San Francisco, and I was accepted to start my residency in psychiatry there. But in the meantime, Harold told me, "Oh, I wouldn't go to California. The best place in psychiatry in the country is Bellevue. You ought to go to Bellevue." So, I went up to New York, saw Sam Wortis and he accepted me on Himwich's recommendation. Instead of going to California, we went to New York.

TB: When did you actually leave Himwich to start with your residency in psychiatry?

AF: In June 1948. Although I did not go to San Francisco, we drove out to California in 1956 and '57. Marcia's brother was living out there. And when I looked at the city, I said to Marcia, "Oh, God, what a mistake I made." I must say that San Francisco is a beautiful city, but so is New York. Anyway, I went to get training at Bellevue.

TB: So, you started your psychiatric residency at Bellevue in July 1948.

AF: I started as a first year resident at \$18.00 a month. But fortunately that was the time of the GI bill and I got enough to live on with some help from Marcia's parents. And Marcia was doing some work, too. It was okay. After I started at Bellevue in psychiatry, I looked around for some research to be done, but I must say there wasn't very much going on, and the residency occupied a good deal of time. While a resident, I spent some time in the EEG laboratory. I was given credit for my time in the army, so I only needed two years to complete my training. During my training, I made contact with Laretta Bender, who was in charge of the child psychiatry service.

TB: She was one of the pioneers of child psychiatry.

AF: Laretta Bender was one of the outstanding child psychiatrists in the country, I would say. She, Leo Kanner, and maybe, a couple of other people were well known even outside of the United States. She had invented the Bender-Gestalt test that is still widely used in the country. She and Paul Schilder had worked with psychotic children, which they diagnosed as childhood schizophrenia. I became interested in childhood schizophrenia and hypothesized childhood schizophrenia and adult schizophrenia were related. Later on, I followed up the children they had diagnosed as childhood schizophrenia; I found that most of them were adult schizophrenics in hospitals or living in the community.

TB: So you worked with Laretta Bender.

AF: She was very much interested in neurological soft signs in schizophrenic children, and perceived childhood schizophrenia as a neuro-developmental disease, a "lag in development." I wrote a couple of papers with her on this topic. She also had written papers with her husband.

TB: Wasn't her husband Paul Schilder, the famous neurologist and psychoanalyst?

AF: Yes. I became also very interested in psychotic children who were damaging themselves. We had several head bangers. One of the kids kept on banging his head so hard that we put a football helmet on him, so that he wouldn't injure himself. I remember reading about Paul Ehrlich in high school and was fascinated by his idea of finding magic bullets for diseases. So I started

looking around to find a magic bullet to treat these children. All we used in these children in those days were paraldehyde and sodium amobarbital that would knock them out. And that didn't seem to be very satisfactory to me. So, I started experimenting with various drugs and that's where my psychopharmacology really began.

TB: So, we are now in mid-1950?

AF: No. Actually '51, before chlorpromazine appeared in the USA.

TB: And you were, in those years, in child psychiatry?

AF: I took my board examination, in 1952, and became first, the junior, and then, the senior psychiatrist on the children's ward.

TB: So, after taking the board examination in psychiatry, you stayed in child psychiatry?

AF: Yes.

TB: You were in child psychiatry in the years when chlorpromazine and reserpine were introduced?

AF: Yes, but not exclusively. I started private practice and saw adult patients as well.

TB: And, you were looking for magic bullets?

AF: Well, I did, and when I attended neurology grand rounds, I learned about a new antihistaminic drug that was found useful in patients with Parkinson's disease and other neurological disorders. The drug produced somnolence and had pacifying effect. So, I thought I should try it because it might be effective also in some of the children I was treating.

TB: What is the drug you are talking about?

AF: It is Benadryl (diphenhydramine). I used it in a few children and it seemed to have beneficial effects. Besides Benadryl, I also used Phenergan (promethazine) and Miltown (meprobamate) soon after they were introduced.

TB: So you used Benadryl in a few children before you used chlorpromazine?

AF: Oh, yes, before we knew even about chlorpromazine.

TB: What about Phenergan?

AF: I used Phenergan after I heard about chlorpromazine. I think it was Squibb or American Home Products that had Phenergan, and I suggested to them that we should try Phenergan in children because it resembles chlorpromazine

TB: It differs by one methyl group on the side chain.

AF: Antihistamines worked in psychotic children. I remember telling that to Himwich, who by that time was in Galesburg, Illinois. After I told him about our findings with Benadryl in children, he tried it in psychotic adults, and it did not work.

TB: So, you were one of the first trying some of the new drugs in children; you were pioneering pharmacotherapy in children.

AF: I was trying to develop it; and I wrote a couple of papers on my findings with several drugs, as for example with Benadryl.

TB: Did Laretta Bender show any interest in your findings with Benadryl?

AF: Oh, yes, she was very much interested in it. As a matter of fact, I was very amused to learn that even after I left the children's service, she continued to use it. The other day, I was talking to a psychiatrist who worked with Loretta Bender after I left, and he told me that she continued using Benadryl, and not just she, but also Barbara Fish and others.

TB: So it was you who established the place of Benadryl in child psychiatry.

AF: Yes. My original findings remained the basis for the use of Benadryl in child psychiatry. However, I must emphasize, I continued my work testing various drugs on psychotic children. In those early days, I conducted controlled studies in collaboration with two colleagues. I checked the records and randomly assigned various drugs and placebo to the children. They were examined by my two colleagues, who reported the findings to me and I collated the results. One of our studies showed clearly that chlorpromazine was superior to Benadryl, although I must say that Laretta Bender was unimpressed with my findings and insisted that in her experience, Benadryl was superior and never changed her mind. The Professor of Pediatrics at New York University (NYU) was very interested in the study and pressured me to have it published in the *Journal of Pediatrics*. That probably was a mistake. It should have been published in the *American Journal of Psychiatry*. However, I continued my studies with various psychopharmacologic agents in children, particularly as new drugs appeared on the market. This continued later at Downstate. I think I made a very important contribution to psychopharmacology in children.

TB: When did you leave Bellevue?

AF: I guess I left in '54.

TB: Why did you leave?

AF: I thought that I had had enough of full time hospital work. So for a short time, I was in private practice while working as an instructor in child psychiatry and doing research at the Columbia Presbyterian Hospital. I was the psychiatrist on the team that was studying the RileyDay Syndrome that was to become known as familial dysautonomia.

TB: Could you tell us something about familial dysautonomia?

AF: This is an inherited disorder present almost exclusively in Jewish children. One of its most distressing aspects is severe vomiting that could lead to dehydration, changes in electrolyte balance, and death. We used to meet once a month with the parents of these children. And one of the parents was a pharmacist, who came to me after one of those sessions and told me about the announcement of a French drug that supposed to be very good for nausea and vomiting. He was wondering whether it could control the vomiting of these children. We were in need of a drug that could control vomiting in the children, so I asked him to bring me some written material on the substance. So, he did, and he showed me a brochure on chlorpromazine. At that time, chlorpromazine was already being evaluated in the United States by Smith Kline & French (SK&F) and I decided to try it in children with familial dysautonomia, as well as my Bellevue population of psychotic children.

TB: You tried it to control vomiting in familial dysautonomia?

AF: Yes, but before doing that I tried to find out what was known about the drug. So I learned that they used it first in general anesthesia. I also learned that there were clinical trials going on in several places with the drug, including on the adult psychiatric wards at Bellevue Hospital. After that, I got hold of chlorpromazine, and in a comparative study, I found it better than Benadryl or Phenergan in the control of vomiting. I thought that chlorpromazine might also be good for psychotic children as well as other disturbed kids, so as I said before, I did clinical research on our Bellevue population with chlorpromazine, as well as other drugs.

TB: So, you were also among the first or might even be the first using chlorpromazine in children. You did this work at the Columbia Presbyterian Hospital in New York.

AF: But also, at Bellevue, with disturbed children. It was about that time that Richard Day accepted the position of Professor of Pediatrics at Downstate Medical Center of the State University in Brooklyn and was looking for a psychiatrist to work on the ward. I was ready to take

a full time job again, so I decided to apply for the job, and I was accepted. I was working in his department from 1955 to the end of the 1950s.

TB: As a child psychiatrist.

AF: Yes, I was the child psychiatrist in the Department of Pediatrics and continued my research in psychopharmacology in children. Then, Dick got me interested in erythroblastosis fetalis in premature children. I succeeded in getting a large grant from NIH to study brain damage in premature infants. In our study, we matched a large cohort of premature infants with full term controls in Bedford Stuyvesant, a black, very impoverished neighborhood, in Brooklyn, and found brain damage in a larger proportion of premature infants than in their full term matched controls. We continued this study for six or seven years and published several papers on our findings. One of the important findings was, as I already mentioned, that among premature infants, more developed brain damage than in the others. Another important finding was in the follow-up of these kids. Bedford Stuyvesant was a very impoverished neighborhood, where the children were growing up in an environment deprived of any intellectual stimulation. The only newspapers these children saw were the newspapers they slept on. And what we found was that three years after they were born, it became evident that the difference in cognitive development between the brain damaged and matched non-brain damaged premature infants growing up in this intellectually deprived environment disappeared. These findings led us to look into how we could enrich the development of these kids; how could we do something for them? Actually, the work we did became noted, more than I had realized. And even about three or four years ago, when I saw Julius Richmond, past Surgeon General, who is a Harvard Professor Emeritus, he said, "Oh, that paper you wrote with Helen Wortis, that showed the terrible effects of impoverishment, of poverty on the growth and development of children; I always use it and quote it." When I expressed surprise, he sent me a recent paper of his quoting our paper. We developed a program on how to enrich the development of impoverished children that we started in Brooklyn, and that continued in New York, after my departure from Downstate to join New York Medical College. To extend our program, we collaborated with people who eventually set up a whole consortium dedicated to this issue of preventing the effects of impoverishment and deprivation on the development of children. Our findings stimulated interest in developing programs even outside of the United States. Some colleagues gave us credit as a precursor of Head Start. We had a colleague, Reuven Feuerstein in

Jerusalem, who developed a whole enrichment program that we were in contact with. So, that was one of my major efforts in the five years I spent at Downstate. I was also involved in other activities at Downstate. I recall that I was running an annual symposium on childhood schizophrenia. It was originally organized by Carl Hirschberg but I took it over when he got sick, and I ran it for about three or four years. I actually just started to put the material of the program together in a book, when I was approached by New York Medical College to become Chairman of the Department of Psychiatry there.

TB: What year was that?

AF: Well, it was the end of 1959. I think it was in the winter. Some of my friends encouraged me, whereas some others discouraged me from taking the job. I was told that it's not the best Medical School in New York, that I would not be able to get support, and that there was no real budget for the Department. And some of the things I was told were true. There had never been a full time Chairman of the Department of Psychiatry at New York Medical College. The previous one was a part time chairman, who had a huge private practice. But I thought of the possibilities of building a Department there and decided to take the job. And so, I began there in September 1960. I brought over the research projects we had been doing on child development at Downstate and addressed myself to the task of building a Department.

The New York Medical College was then in the Flower Hospital at the corner of 106th street and 5th Avenue. Our primary teaching hospital was the Metropolitan Hospital. Both the Medical School and Metropolitan Hospital were in East Harlem, which was, and still is, probably the most impoverished area of New York, with the highest incidence of drug abuse, particularly heroin addiction and severe alcoholism. So I decided that we should focus on drug abuse. And it just happened that at the time the city had approached a number of the teaching hospitals and medical schools, about doing work on drug abuse, and they all turned it down. It was considered sort of dirty work. But, we accepted the challenge and set up a detoxification unit at Metropolitan Hospital for adults and adolescents. There was great publicity, at the time, about drug abuse in adolescents. And so, we set up a ward for adolescents. When I started, neither Metropolitan Hospital nor Flower Hospital had an in-patient psychiatric service. So the addiction services in those hospitals gave me a base to operate from. I also inherited a very small outpatient clinic that had very few patients because, as it turned out, the nurse who received the new patients felt that anybody who didn't speak good English could not profit from psychiatric care. Since most of the

population in the area were Puerto Ricans who had little English, she turned them all away. Anyway, we changed that, and in about a year, our Outpatient Clinic visits went from about five thousand up to about seventy thousand. That was a very active service. And we developed several programs, over the years, for drug abuse. First, as I said before, we set up a detoxification unit, then we realized that a detoxification unit alone does nothing but get the patients out to get them back again, it was a revolving door. So, we became very much interested in community mental health. We felt that the community approach was very important, not only for drug abuse, but for all psychiatric disorder. So, even before President Kennedy made his address in 1963 about the importance of community mental health, we already started a community mental health program. I had a team working in East Harlem. Then, we started to develop educational programs for neighborhood groups, particularly for schools in regard to drug abuse. We were very active. I participated in a White House Conference on drug abuse that was run by Robert Kennedy. It was a very rewarding period, particularly in the Kennedy era. Marcia, my wife, who is an economist, a labor economist, worked in those years on the transition from school to work, in juvenile delinquency and other similar areas. She was a consultant to Robert Kennedy and I will always remember that in the middle of the night, suddenly the phone would ring and they'd say, "This is Attorney General Kennedy's office, is Marcia there?" Usually, instead of going and looking up records, they'd call Marcia as the expert, and she would tell them. Then we'd go back to bed. So anyway, it was a very exciting period of time for all of us. There were those two programs in drug abuse, but at the same time, we had interest in community mental health that was reinforced by Kennedy's address. And we applied for a grant to build a new Mental Health Center. We already had two wards in the hospital for drug abuse and we now managed to get, with some maneuvering, two more wards for adult psychiatry. The Dean was helpful, in spite of the fact that he had to take some beds away from other services. I remember the Professor of Obstetrics and Gynecology telling him, "You'll turn over any wards over my dead body." Then, a reporter from one of the newspapers went to Kings County Hospital and wrote a huge expose about how miserable the treatment was there. Mental hospitals were overcrowded and the city had to respond. This gave me an opportunity to put in my two cents and they told me that they were going to build a Psychiatric Hospital at Metropolitan Hospital. But then, there was no money for it. This was in the Kennedy era, after passage of the Comprehensive Community Mental Health Centers Act. We applied for a construction grant and we got it. So we built a Psychiatric Institute with a Community

Mental Health Center. And then, we put in for a staffing grant, which we were awarded. Now we were in business. Since we were involved in drug abuse and interested in finding some treatment for opiate addicts, Abe Wikler invited me to Lexington for a discussion. He thought that the opiate antagonists were the answer. He had the theory that drug abuse is a conditioned response. He thought that the initial effect of a drug, like heroin, was reinforced by subsequent use, and especially when in the withdrawal period the discomfort disappears by taking another dose. He was providing some evidence for his theory in animal experiments. The conditioned aspects of addiction to heroin and other drugs in Wikler's theory were lasting effects, if left untreated. For example, let us say someone from East Harlem was arrested for a crime and up in Sing Sing would be withdrawn from all drugs he was using. But then, two or three years later he is discharged, and, when passing by in Harlem his old neighborhood on the train, he would suddenly develop withdrawal symptoms so severe that he rushes off the train to look for some heroin. So, anyway, Wikler's theory made, I thought, a lot of sense, and he was working, at that time, on cyclazocine, an opiate-antagonist. I became interested in this opiate antagonist and we agreed that I would try it out. It just happened that Max Fink, who had been in St. Louis and was very unhappy there, came to me and asked if I had a job for him. So, he joined me and although his life-long interest was ECT, he agreed to work on drug abuse, while, of course, he continued his research with ECT. We started a program on cyclazocine and the substance proved to be an effective opiate antagonist. The theory for cyclazocine treatment was that if you could prevent any response to heroin over time, the conditioned response would become extinguished. Cyclazocine worked all right as an opiate antagonist but it had side effects, like vivid hallucinations in some subjects that prohibited its continued use. We also noticed that some individuals had high spirits and euphoria while on the drug. We thought cyclazocine might be an antidepressant and thought to try it in adults and also in children. I used antidepressants in children, and especially Tofranil (imipramine), in spite of the commonly held belief, at that time, that depression in children did not exist. But the idea of using cyclazocine in depression was abandoned because of the hallucinations produced by the drug, which could not be overcome.

TB: Did you study Tofranil in children?

AF: I did.

TB: It was probably the first study on children.

AF: Probably.

TB: And you also did some early clinical studies with opiate antagonists.

AF: Yes. And, the men taking cyclazocine told us that it acted as an aphrodisiac. They said, "I'm getting up in the morning with an erection like I haven't had since I was fifteen years old." But, we figured that heroin inhibits sex, and by using an antagonist, the effects of heroin was wearing off and that was what they experienced. So, anyway, we weren't getting any further with cyclazocine, although we felt that it was working. Then we discovered naloxone, and Max Fink and I did a series of experiments with naloxone. In some of these experiments, we injected heroin first and saw no response to heroin injection. Then, we did the opposite, injecting heroin followed by naloxone. The heroin rush disappeared after the injection of naloxone. So, we felt that it should be an effective drug and started to use it in drug addicts.

TB: What period of time did you do the work with opiate antagonists?

AF: We're getting into the late 1960s. In those years, I felt that drug abuse has a biological basis. It seemed that from all practical purposes every young boy in East Harlem was trying heroin, but only a small percentage of them took it again and became addicts. Well, it was suggested that there might be social pressure on the particular child that becomes addicted. Another hypothesis was that a child who has a stable family relationship or a close relationship with a teacher or a priest, would be able to resist further use. But I felt that there must be a biological aspect to drug addiction, a vulnerability or susceptibility to drug abuse, so I was looking around for various sorts of biological approaches to treatment at the time. When I saw Wikler, and when Max joined me, I think it had to be in 1965 or '66, that we started an active program in the pharmacological treatment of drug addiction.

TB: So you found that naloxone was an effective agent.

AF: It seemed to be that naloxone would be an effective agent, but its effect only lasted three to four hours. So, we started looking for ways of prolonging the effect of naloxone, by mixing it with other substances. I remember, that the ALZA Corporation, on the West Coast, specialized in modifying drugs so that they would have longer periods of action, but they had nothing to offer that would prolong the effect of naloxone. In spite of the problem of its short duration of action, we continued using naloxone. But then, the ENDO Corporation that made naloxone was sold to DuPont, and DuPont decided that there was no money in naloxone and to our consternation,

stopped manufacturing it. So we contacted one of the science writers of the New York Times, and he wrote a column on “The great possibility of a drug for drug abuse, that’s being eliminated by DuPont.” The next morning, after the column appeared, I got a call from DuPont that they could give me another drug that we could use instead of naloxone. So, then, naltrexone came along that was longer acting than naloxone. We were among the first to use it, and, this takes us well into the ’70s. And, during the 1970s, we also found β -blockers useful in the treatment of addiction.

TB: So, you had Max Fink working in your department.

AF: Yes, and I should have mentioned that when I became Chairman, I made two important recruits. One was Lothar Kalinowsky, who was instrumental in introducing ECT and other physical therapies in the USA, and the other was Silvano Arieti, a distinguished psychoanalyst. Lothar turned out to be a wonderful friend. I have enormous regard for him and his wife. Soon after Kalinowsky joined the department, there was a meeting in New York organized about Sakel’s insulin coma therapy, with invited participants from all around the world. And during the meeting, Lothar told me that there were two people among the guests who wanted to travel around the United States. Then he said, “You know they need about five hundred dollars, each, and I have a man who will donate it; but he wants to give it in a way that he can take a tax deduction, so can you handle that for him?” I said, “Sure, no problem, have him make the check out to the Department of Psychiatry.” And then I said, “Why don’t you ask him for money so we can have distinguished psychiatrists from abroad give lectures here?” So Lothar said, “Don’t be ridiculous, he’ll never do that.” The man’s name was Goldman, a former patient of Kalinowsky who was grateful to him, so, I said, “You tell him we’ll name the lectures ‘The Goldman Lectures.’” So Kalinowsky went to Goldman immediately, and called me at midnight all excited, and said, “You were right, when I told him that Dr. Freedman has this crazy idea of having lectures from distinguished psychiatrists from abroad, and thought maybe you’d support it, he responded, ‘well, that’s a good idea, if you like, I’ll give you five thousand dollars to start with,’ and when I told him, I’m sure you wouldn’t be interested, but he wanted to name the lectures, The Goldman Lectures, he responded, ‘Oh! I’ll give you ten thousand dollars every year.’” So every year, we got the money as long as Goldman lived.

TB: When did this happen?

AF: Mid 1960's. It happened soon after Lothar Kalinowsky joined me and became a professor in the Department. The Gracie Square Hospital, where he was doing most of his work, was having troubles and they were talking about selling it, and the New York Psychiatric Institute he was affiliated with, never really did very much for him. We became very dear friends and the Goldman Lectures were wonderful. We invited famous psychiatrists from Europe and Asia to lecture and we not only paid them for their trip, but we gave them extra money to travel around the United States. We had prominent psychiatrists like Pierre Pichot from France, Hanns Hippus from Germany, and Paul Kielholz from Switzerland, here. We also had Manfred Bleuler from Burgholzli and Martin Roth from the UK.

TB: At the time you became chairman, we were still in the psychodynamic era of psychiatry in the United States.

AF: I had psychoanalytic training and got a certificate, in 1955, from the William Alanson White Institute. And I was a member of The American Academy of Psychoanalysis. But I always adhered to an integrative approach, that behavior is based on dynamic interplay between environment, experience, and biology. I'm very committed to that approach.

TB: Did you promote integration in your residency program?

AF: Yes, of course. We had no residency training when I arrived, but within a year I got one started, and it proved to be very successful. We put great emphasis on our undergraduate program, and for several years our students ranked number one in the National Board Examination in the country. So we had a very good teaching program. Before I moved to New York Medical College, I was thinking about editing a multi-authored book on child psychiatry. But, then, I started to think about developing a comprehensive textbook of psychiatry that would be multi-authored. I invited Harold Kaplan to join me in doing it. So, we started to look for a possible publisher. It was hard to find one because they didn't think a multi-authored text in psychiatry would work. After several publishers rejected it, Williams and Wilkins agreed that they would take it up. We understood that, at first, their committee had turned it down, but then they decided maybe it's worth a try. So, they were only going to publish five thousand copies, but, then, before it was published, they decided to increase it to ten thousand. Eventually, they sold somewhere around fifty-five thousand. The book was a smashing success.

TB: What year was the first edition published?

AF: 1967.

TB: '67. If I remember well, that year every psychiatric resident received a copy of it from Hoffmann LaRoche.

AF: What was particularly gratifying to me was that it became the textbook for the country. I remember Fritz Redlich telling me, "Your book is going to kill my book with Danny Freedman and also Larry Kolb's book." Both books remained in circulation, of course, but we dominated the market. But, in addition to the United States and Canada, the book was used all around the world by people for years to come. And in 1988, to leap ahead a little, when I was in Melbourne, giving a talk, Professor Sing, who's now the Chairman of the department there, got up and he said, "I want to personally thank Professor Freedman for being an enormous help to me, when I was studying to take the Royal College Examination; his book came out at the time and I just studied it backward and forward several times, and I passed without any trouble. I want to thank you for it." So, my identity for a long time, it still is in many ways, particularly abroad as well as in this country, rests on the book. When I meet people they frequently say, "Oh, you're the Freedman of the *Comprehensive Textbook*."

TB: The Comprehensive Textbook has been very extensively used.

AF: I was especially pleased when I learned that it was well received abroad. Apparently, many of the known European psychiatrists thought a textbook of an American would be purely psychoanalytical and were surprised to see a textbook with chapters on biological aspects of psychiatry by Seymour Kety, on psychopharmacology by Jonathan Cole, on ECT by Max Fink, and others, edited by an American. It was a book that reflected my philosophy; it was eclectic, with sections ranging from various psychoanalytic theories and community psychiatry to drug abuse. So, the Europeans were impressed.

TB: It had an impact on teaching psychiatry at least in North America.

AF: Another thing that happened, during my first decade at The New York Medical College, was that my very good friend Leon Eisenberg became Chairman at Massachusetts General Hospital and asked me to go to Harvard as professor. Well, I evaded the issue and foolishly decided not to take the job. So, anyway, that's another one of those things. But, I was involved in so many new things at the time; we were building a new building, I had many programs, I had just recruited Roy Johns, from Rochester.

TB: What years are we talking about?

AF: 1967–78.

TB: So you also had Roy Johns?

AF: We had him for about, probably ten years or so.

TB: So you had a program in neurophysiology?

AF: Yes. We had many programs including a program in psychology.

TB: Then, in the early 1970s, you became a national figure.

AF: In 1970, I became President of the American Psychopathological Association, after serving for years on many of their committees, and just as my term was terminating, in 1971, I was elected President of the ACNP. During my Presidency, I was trying to make substance abuse a legitimate subject of psychopharmacology and I don't think I succeeded very well, even though I spoke about it in my Presidential address, and I turned out a volume with Seymour Fisher on drug abuse. I was also trying to democratize the ACNP, get more people involved, and maybe, to have regional meetings organized several times a year. I guess some of that has occurred over the years. And, then, in the fall of '71, I was approached to run on petition for President of the APA. Previously, the APA had been a closed corporation; and the hierarchy would select the person, usually someone who had been Secretary or Vice President, to become the President. He (always a man) was proposed on a single slate and was elected without any opposition. At that time, there were lots of things going on about the Vietnam War and, also, the gays were beginning to assert themselves, and were looking for recognition in the APA. So, the Committee of Concerned Psychiatrists was formed. It was actually that Committee which approached me about running for President. And, my immediate response was, "Don't be ridiculous!" First of all, I didn't want a job that would take me away from work that I thought was more important. Secondly, the medical school had just set up a sabbatical program, and I was the first to be granted a sabbatical. Third, I had plans to do a study on alcoholism and drug abuse that year with WHO in Europe and I was looking to travel around Europe from Paris. Thus, the school had approved a sabbatical program and I would have a sabbatical year. So, I said, "No, I can't do it, I'm just not known enough around the country," repeatedly. But every time I turned it down, somebody else would call asking me again and again to accept it. Then, I got a call from Lester Grinspoon, and he said, "Look you don't have to worry about your sabbatical, because you'll never win, but it's very important for the movement, for the cause, for you to run. You'll get forty five percent of the votes, and then

you'll be able to do what you were planning to do, and you'll have also done a great service." So, I said, with my luck, I'll probably win and I won't be able to go on sabbatical.

Anyway, that's the way it turned out. And on the first ballot I was two points ahead, and I won by two votes. I was running against your fellow Hungarian, whatever his name (George Tarjan) at UCLA, in California with Jolly West. Anyway, Jolly West and the others demanded a recount, and I won by three votes. I increased my margin by fifty percent. So, anyway, I became President in May 1972, and that was in Dallas. The APA has been an important part of my life. I had been active for a long time in the local APA, before I became President of the District Branch of New York that was probably the largest in the country. And then I became a delegate to the Assembly for the area of New York State before I was elected President. So, I had been active in the APA, but then as President Elect, I became even more active.

TB: Did you take your sabbatical while President or after your presidency?

AF: No, I never got a sabbatical. I had to give it up and then the school cancelled it. It turned out that a lot of the people on the faculty were supported by city money, at the city hospital, and the city said, if you don't work you don't get paid. So that meant that the school would have to pay for sabbaticals for all these people who were paid from Metropolitan Hospital money. They decided they couldn't afford it.

TB: So now we're in the early 1970s, when you became President elect of the APA.

AF: It was a little rough at the beginning, because I was an interloper in the boys club. But everybody was quite helpful, especially Walter Barton, the Executive Director, at the time. During the year I was President Elect, I went around the country lecturing to district branches, and meanwhile I kept the ball rolling at the department. In May 1973, in Hawaii I became President, and my presidency ended in 1974 in Detroit. We achieved during my presidency, a number of things that I think are noteworthy. First of all we started with a reorganization of APA because I felt there was unrest in the Assembly, a feeling that they were being denigrated. We had our first conference about the reorganization in the Keys, in Florida, the "Key Conference." It took several years' negotiations, so, before the re-organization was completed and the Assembly received more powers, we decided to have multiple slates and not just one slate for election. The APA since had another major re-organization but that was necessitated about two years ago by the tax laws.

TB: Having multiple slate for electing officers was in important step in the democratization of the APA.

AF: Another major achievement during my presidency was on the status of homosexuality. In December 1973, the Board of Trustees passed a resolution to delete homosexuality from the *Diagnostic and Statistical Manual of the Association (DSM II)* and declare that homosexuality was not a disease. We had very strong opposition from the psychoanalysts to pass this resolution. One of the leading psychoanalysts, Irving Bieber, who spoke up, was a member of my department. They were quite aroused because they had published papers and books about homosexuality being based on having an aggressive mother and a passive father. There was also another psychoanalyst who spoke up, and I found that quite surprising because it was well known that his son was homosexual. I guess nobody asked him whether he considered himself a passive father. But, to make a long story short, the psychoanalysts were so upset that they organized a referendum that was defeated by a majority vote of sixty against forty, that was a major victory. It might be interesting that one of my sons, who lives in Washington and is the Washington Correspondent for the Hearst Newspapers, informed me that the Washington Post, in 1999, when identifying the most worthy story for each day during the 20th century, selected for December 13, 1973, as the most worthy story for the day, the APA's declaration that homosexuality is not a disease. That was the most important story, for that day, for a hundred years! I brought this to the attention of the Board at the Board of Trustees meeting and spoke also about it to Jim Krajewski, who's the Editor of *Psychiatric News*. And the next thing that happened was that his Associate Editor called and asked me to write it up for them. So in September, there was a historical note written on it by me, I don't know if you saw it. That was another important achievement during that year. There are also several other things that happened during my presidency.

TB: Tell us about them.

AF: In my presidential address, I dedicated a large section to the integration of the different approaches in psychiatry, and I made a point about ethical issues and the abuse of psychiatry.

TB: Weren't you in the Soviet Union on a mission to try to find out what was going on?

AF: Oh yes, I went to the Soviet Union in October or November 1973 and we visited the Serbski Institute that was thought to be the place where most of the abuse went on. We were fighting all

through our visit with the Russian psychiatrists but with some of them I became good friends. One of those psychiatrists, whom you probably know was Marat Vartanian.

TB: Yes, I worked with his brother Felix when I was consultant at WHO.

AF: After my Presidency, I was elected to the American Board of Psychiatry and Neurology and served there for eight years. I was working closely with Marc Hollender on the Board and we were involved in a lot of educational programs. It was called to our attention that there were very few women in psychiatry, and that it was difficult for women to get residency-training because many of them were married and had young children. So we developed a program, a mother's residency program, which instead of three years was four years, they could take the summer off, and they could stay home when their child was sick and so on. And the people covering for them were not resentful. Actually, the program worked out very well; we got a lot of very, very fine women. A couple of them were trained in Pediatrics but had to stop practicing because they had two or three children. And then, when they heard of this program, they decided to get trained in psychiatry and eventually they became child psychiatrists.

TB: Didn't you get also involved in the APA with international affairs?

AF: Yes, and after my Presidency, I became chairman of the Committee on International Affairs. We organized joint meetings after our annual meetings with sister organizations. We had a meeting in the 1960s and 1970s with the Australians after the annual meeting in San Francisco, and with the Irish after the annual a meeting in New York. I also remember organizing with Pichot a joint meeting of the American and the French societies. I was the Chair of the Committee on International Affairs, when in 1977, Sadat made his trip to Jerusalem and made his speech in the Knesset, saying, "We should make peace, we are after all, all brothers." I was fascinated by his speech and we decided that we would go to Egypt and to Israel, survey the situation and see whether we could help in making advances. So, we went to Egypt with great enthusiasm and we were warmly welcomed. We attended Sabbath services at the Great Temple and Synagogue in Cairo. And then, we went to Israel, came back to Egypt, went again to Israel, and everything looked wonderful, but ultimately, it didn't quite work out. The project continued until interest in our activities was lost and we couldn't raise any more money.

TB: Was this about the same time when you became involved with the American Committee on the Prevention and Treatment of Depression?

AF: That started much before. In 1972, I attended the CINP Meeting in Copenhagen and went out to dinner with Pierre Pichot to the Tivoli Gardens, and while we were walking to find a restaurant, we ran into Paul Kielholz and Hanns Hippus. So, we decided to have dinner together, the four of us. It was at that dinner that Kielholz invited me to attend in January 1963 the meeting of the Committee of Prevention and Treatment of Depression (PTD) in St. Moritz. Fritz Freyhan was the chairman of the American PTD Committee for many years and after his death, I succeeded him.

TB: I remember that very well because I was a member of that Committee.

AF: I was also on the executive committee of PTD, as well as on the jury of the Anna Monica Foundation Award selecting the most important contribution in the year to the understanding or treatment of affective disorders. All those were very rewarding experiences that slowly came to an end after Paul Kielholz died in the mid-1980s. I did a lot of traveling and lecturing around the world. I was elected a visiting professor to Australia and New Zealand and that was a great experience.

TB: Where did your support for the visiting professorship come from? I'm asking this because I had a visiting professorship in 1975 to New Zealand that was supported by Pfizer.

AF: It was awarded by the Royal College of Australia and New Zealand and supported by Roche. I traveled with my wife and we stopped off in Jakarta. I lectured there and we were entertained. From Jakarta, we went to Bali, and then all around Australia, starting in Perth. I also had the opportunity to run a big workshop for WHO in Changsha, China, on psychiatric education, that gave us an opportunity to travel around in China.

TB: When was that?

AF: In 1982. We made also other visits to China. And, we also went to Japan, where I became good friends with Professor Nishizono. Then, in 1993, I went to Japan and China as a consultant for WHO. In the early '90s, I was appointed Honorary Professor of Psychiatry at the Hunan Medical School in Hunan, China.

TB: Weren't you interested also in psychiatric diagnoses in early 1980s?

AF: Yes, in the 1980s, we published a small volume that was rather critical about many of the *DSM-III* diagnoses. I felt *DSM-III* was leading to a proliferation of psychiatric diagnoses, and rather than splitting disorders further and further, it would be important to integrate diagnoses,

bringing them together. I was also involved, on Pierre Pichot's invitation, in a conference in Paris that dealt with the French translation of *DSM-IV*.

TB: If I remember well, you were very much involved in editing journals in the 1980s. AF: I had been on the editorial board of several journals. One of them was *International Journal of Pharmacopsychiatry*.

TB: That was to become *Neuropsychobiology*.

AF: And, I was also on the editorial board of the series *Modern Problems of Pharmacopsychiatry*. Then, I was approached by Elsevier, asking whether I would like to edit a new journal that they would support, and so, I started *Integrative Psychiatry*.

TB: What year was that?

AF: In 1982.

TB: It was an excellent journal.

AF: I tried to promote in the journal the bio-psychosocial model, the integration of experience and structure into one whole. I continued with *Integrative Psychiatry* until I retired, in 1989 or 1990. But then, I became interested in continuing it, and so, we started again around 1992, but unfortunately, I had to stop because of health problems.

TB: Weren't you also involved with the International Society of Political Psychology (ISPP) and the journal of that Society?

AF: I was actually not a member of the ISPP but I had several friends there, particularly one man who had been in the State Department, who approached me to become editor of the journal of the Society. It was not really a journal that they had, but I was interested, and turned what they had into a real journal. I must have been editor in chief of that journal for several years, until 1989, when I retired. In appreciation of my services to the journal, ISPP established an Alfred M. Freedman Award annually, for the best paper that was presented at the annual meeting of the Society.

TB: What about your research in the 1980s?

AF: One area of particular interest during that period was combined treatment with psychotherapy and drugs. I delivered a paper on that topic at one of the St. Moritz meetings, in which I pointed out that combined treatment of depression with psychotherapy and antidepressants is superior to either of these treatment modalities alone. Later on, Jerry Klerman and Myrna Weisman wrote

several papers on the superiority of combined treatment with psychotherapy and drugs in depression. And, I was doing research with Turan Itil, who also joined me shortly after Max Fink left. He set up a computerized EEG laboratory in Valhalla.

TB: In Valhalla?

AF: I have not mentioned it that the medical school, in the early 1980s, decided to move the school to Westchester, Valhalla. This was the time that Roy John left. We lost our old facilities and it took a long time to develop our facilities in Westchester. But, we still continued with several research programs and I even extended our activities to studying psychotropic drugs in medically ill patients. I received a grant for that, and it was Mike Bloomfield who carried out the research in the program. We also did a study with β -blockers and found them of some use in narcotic addiction.

TB: What did you work on with Turan Itil?

AF: I had several projects with Turan Itil. One of them was related to the AIDS outbreak in those years. We became interested whether one could detect by EEG, early changes in the brain that would indicate they were going to develop dementia or other mental changes. And, we found that one might be able to detect, by EEG, early changes that predict the development of mental changes in patients with AIDS. At the same time, other people in the Department were using psychological tests that would predict the development of mental changes in the same patients, and the findings with these tests corresponded with the EEG findings.

TB: Did you have any other project with Turan?

AF: I was also working with him on natural substances, using his expertise in quantitative EEG and my connections in China. It was in the course of this research that we identified Ginkgo Balboa as a possible remedy for the treatment of Alzheimer's disease. We tried to get a grant for testing it but did not succeed. Finally, Turan found that Schering, a German corporation, was interested in it.

TB: How did you proceed with Ginkgo?

AF: We conducted a multi-centered study with Ginkgo in Alzheimer's disease. It was a very carefully designed study, and Le Bras, who at the time was still Turan's son-in-law, wrote up the findings.

TB: When was that?

AF: 1997. We published the paper in 1997. To my knowledge it was the only double-blind, carefully done and properly analyzed study on Gingko. And our findings indicated that Gingko would probably delay development of Alzheimer's by six months. It's not enormous, but still significant. And further work is going on to try to isolate the various constituents of Gingko. I'm no longer involved in that.

TB: Yes, but you were instrumental in getting the substance from China and opening up that research.

AF As a matter of fact, originally, I was the principal investigator.

TB: Were you involved in any other research in psychopharmacology after Gingko? AF: I would have done more, but in late 1989, I diagnosed myself with cancer of the breast and was operated on. Then, by the time I recovered from that, I was diagnosed with cancer of the prostate. That inhibited my activity a great deal for a couple of years and when I thought I was improving and getting better, in 1994, I had a reoccurrence of my cancer of the prostate. So all these interfered a lot with my activity, but we still, in between my breast cancer and my prostate cancer, went to Casablanca and made a trip to Morocco. We were invited by a good friend of mine, Driss Moussaoui.

TB: Isn't he the chairman of the Department of Psychiatry in Casablanca?

AF: Yes. I first met Moussaoui when he was still a very young man working with Pichot. He came to New York and Pichot told him to drop in to see me. It was in the middle of winter, he had no coat, and he had very light shoes on. I tried unsuccessfully to persuade him to borrow one of my coats. Then, when we got to Paris some months later, Pichot sent Moussaoui to meet us at the airport at five o'clock in the morning. He has remained a very good friend. We exchange email regularly. He is a very, very nice guy. Then when we came back, I was tentatively diagnosed with cancer of the prostate, but the first biopsy was negative. But then, my PSA was increasing, and when they did a more extensive biopsy, they found cancer in both lobes. I selected to have X-ray treatment, because at that time I was already seventy-three. The surgeon said he had operated on older people but I was of the opinion that if you're over seventy, you should not have surgery. I don't know whether that was a mistake or not. Then, in 1993, we traveled around the world. We started at a meeting in Dublin, on psychosocial rehabilitation. Then, we attended a meeting of the PTD, in Prein, near Munich. From Germany, we went to attend WHO meetings in Fukuoka,

Beijing, and Changsha. And then, we went to other places in China. In the next year, in 1994, I was invited to a meeting outside of Thessalonica in Greece. From there we made a tour of Anatolia, sponsored by the American Museum of Natural History. It was on that train tour that it became obvious that my wife, Marcia, had some heart troubles; she couldn't climb the hills. After we returned home, her heart condition was diagnosed, but still, she remained active. So, we went to Santa Fe to the Opera and then visited friends, in the mountains of Colorado. That all went okay, except Marsha had some trouble in the higher altitudes. She welcomed the experience but realized that probably she would never make a trip like that again. Then, after we came back, in December 1994, I was diagnosed with a recurrence of my prostate cancer. Still, in 1995, we went abroad again, and that was the last trip we made, because in 1997, I was diagnosed with lymphosarcoma of my thigh, and Marcia, with Parkinson's disease. So, we've been quite inhibited in our activities. This is why I have not continued the work with Gingko and done no other research in psychopharmacology. I told Turan that I would like to see *Integrative Psychiatry* continued, but I told him also that he would have to do all the work. But he got too busy doing other projects, so we closed the journal.

TB: You also founded with Turan the Academy.

AF: Academy of Psychiatry - Academia Psychiatrica.

TB: Yes.

AF: That was flourishing, but again I was confined by my illness and Turan had a lot of other things to do, so gradually, after great promise, the Academy sort of subsided. I am also Vice President of the American Division of an International Foundation for Mental Health and Neurosciences that was founded by Jean-Paul Macher in Rouffach. Do you know who he is?

TB: Yes. Are you still actively involved with Macher's Foundation?

AF: We just had a meeting in October.

TB: In Rouffach?

AF: No, here in New York. See we must have meetings of the American Corporation. I was president of the meeting in Rouffach, few years before, and Macher already asked me to come back there next September.

TB: So, they have a meeting annually?

AF: They have an annual meeting, usually in September. Have you ever attended?

TB: Yes, I have attended several times.

AF: Wonderful food.

TB: Yes.

AF: And a good meeting.

TB: So what are your current activities?

AF: Well, I have maintained my interest in various basic science and clinical endeavors but I don't have the hands on relationship at present with any of the projects as I had with Gingko. So my interest has turned to areas of concern. One is the whole issue concerning capital punishment. I've been working on that with Abraham Halpern, who's a forensic psychiatrist, and was a member of my faculty. We first started out when the AMA was changing its regulation for psychiatry, which would open up many avenues for psychiatrists to participate in executions. We fought against that, and I was able to persuade the Board of Trustees of the APA, that they should not approve the AMA resolution. I participated in the debates of the APA resolution at the annual meeting and we wrote several articles on our position. We were concerned about the resolution because we are opposed to capital punishment. I think it's primitive and barbarous to put anyone through that. But the possibility of abolition of the death penalty in the United States is very remote. There's too much support for it. Anybody, like Mario Cuomo, the former governor of New York, who ran for re-election and stated, "I'm opposed to capital punishment," was defeated. The American Bar Association, in 1997, passed a resolution, calling for a moratorium on the death penalty, which we thought was a great idea. They pointed out all the inequities, like discrimination; essentially poor people are sent to death without adequate legal representation. They also pointed out the big variation between the different states. Texas executes a lot of people. So does Florida; whereas other states have very few executions or none.

So, we thought that was a very good issue, and we've been working on getting a moratorium resolution through the APA first. We started at the District Branch at Westchester, and then, the New York State, and finally, we got it approved by the assembly last June. Then, it went through the Council on Law and Psychiatry, and just last week, at the Board of Trustees meeting, they approved it. But by the time it was approved, it has been rewritten to the extent that it will have to go back to the Assembly for final approval. This will be next week. So I hope it will all go through and then we'll get started on the AMA and other societies to get them to approve of

the moratorium idea. This is one area I've been involved in the last year. And I've been on the Ethics Committee of the APA, the Ethics Appeals Board, a sort of Supreme Court of the Ethics, of APA, for many years. So I keep busy.

TB: So, it seems you are busy and are doing things you are interested in. It is remarkable that in addition to your varied activities you had time of publishing the most comprehensive textbook of psychiatry ever written. Is there any other book you have written or edited you would like to comment on?

AF: Well, there's a volume I did with Seymour Fisher that I referred to earlier, on drug abuse, which was an attempt to get the ACNP more interested in drug abuse. I wrote a paper in it about the number's game that Presidents like Nixon were playing. When politically correct, they declare a war on drugs, and after spending a billion dollars on it, the numbers of those using drugs like heroin are slightly decreasing, say, two to three percent. Then, when everything quiets down, they come back up again. There is an actual fluctuation in the use of drugs like heroin, and now, we recognize that the billions of dollars that have been spent on drug programs have been a waste.

TB: During the many years of your activities, you were the recipient of many distinctions.

AF: I got an award from the APA and from the University of Helsinki. Then, I got a medal for my activities in political psychology. I also got the Wyeth Award from the WPA for my contributions to international psychiatry. It was a nice award, because it had ten thousand dollars attached to it. The Mental Hygiene Association gave me an award and the county executive, of Westchester County declared a day in my honor. The New York tabloid, the *Daily News* did a study of psychiatrists in New York City and they decided I was the outstanding Psychiatrist in New York. Of course, in their usual tabloid fashion, they labelled me the "Super Shrink," the most distinguished "Shrink" in New York. So, that was fun. After I received that award in the mid-seventies, my two secretaries bought t-shirts that said "Super Shrink" on it. I received many other awards that are listed in my CV.

TB: As one of the pioneers of psychopharmacology in child psychiatry, how do you feel about psychopharmacology today and about the future of it?

AF: Well, I think psychopharmacology has a promising future. I have appeared at various times, before groups that were, even if not hostile, but not in favor of the use of drugs. I usually tell them if they had seen Bellevue Hospital in New York, in 1948, when I started my residency in

psychiatry, they would have an appreciation of what the new drugs did. There was a pervasive smell of formaldehyde, mixed with urine and feces, that hit you when you entered the disturbed wards with patients wandering up and down babbling in camisoles. It was really bedlam. We cannot emphasize sufficiently the enormous contribution psychopharmacology has made to the care of the seriously mentally ill. In my presidential address to the APA, I emphasized that we have to pay attention to the hospitalized and seriously mentally ill patients. The new drugs made it possible to provide care of the mentally ill in the community, but to do it properly, we need to have support for it. So, there have been enormous changes already in this country and also in other countries in the treatment and care of psychiatric patients as a result of the introduction of the new drugs. There has also been a steady progress in the development of new drugs. And, we are now entering a new era! I'm just very sorry that I'm too old and too ignorant to participate in all the molecular and genomic developments that are taking place, which are leading to a new era in which drugs would be designed to cure selectively specific syndromes or defects, either genetic or biologic. Currently, we see the same problem with psychotropic drugs as we see in cancer treatment, which I have become too familiar with, that the chemotherapy that doesn't act selectively on a particular cell may also kill the heart muscle as well the cancer cells. So, to have psychotropic drugs that would act selectively will be a great achievement.

TB: So you foresee that we will have drugs that will act selectively on distinct mental pathologies.

AF: Another area that I have been concerned with, and peripherally involved with, is the bringing of the new treatments of the mentally ill to developing countries. I have been interested in training people in developing countries to recognize, diagnose psychiatric syndromes, and to treat them properly with the use of new treatments and especially with the use of new drugs. This represents a difficult problem in terms of whom to train, because in countries like Botswana and some other third world nations, there might be one trained psychiatrist for the whole country. The economic aspects of treatments would also need to be addressed. Many of those countries can't afford expensive drugs, as for example the new atypical antipsychotics, and the teaching must get through the message that there is no reason to believe that without some of these new remedies they can treat their patients properly. Haldol is still just as good of a drug as any of the new atypicals. It really works. I feel strongly that everyone should have access to treatment, and that optimal treatment could be provided with affordable drugs.

TB: So you feel that it would be important to teach people in developing countries about the proper use of psychotropic drugs without raising unwarranted expectations about unaffordable new drugs. I understand that you feel strongly that everyone should have access to optimal treatment.

AF: Oh, yes.

TB: Is there anything else you'd like to see happen in psychopharmacology or psychiatry?

AF: Well, I'd like to see that the treatment of the mentally and physically ill is based on the same principles. I would like to see that there is no discrimination, financially and otherwise, in the treatment of the mentally ill. After all, WHO studies have shown repeatedly that depression, and mental illness in general, are becoming the leading causes of incapacity in work. So, I would like to see greater attention and greater respect, in regard for the mentally ill, in general. I am particularly concerned, as I always have been, with the issues of development in the child and the mental health of children. And I'm aware that our knowledge of child development and the neuronal changes that take place in the brain during childhood and adolescence are still insufficient to identify the factors that are significant in this function and maturation. In the recent issue of *Science*, I was very intrigued by an article in which it was pointed out that it is now recognized that neurons can regenerate and proliferate, and, that the failure of cells to proliferate in the hippocampus may be involved in the pathogenesis of depression. I found especially interesting the findings, reported in this article, that both the antidepressant drugs, as well as ECT, stimulate the proliferation of cells in the hippocampus. So if this is the case, then you have something to hang on in depression research. The usual way of testing an antidepressant drug is really pretty far-fetched, but if you have something specific, like cells in the hippocampus, you really have something to go on. So, that's the sort of thing that interests me a great deal. What can be done with genomes, you know, that's also very fascinating. Genetics and psychiatry, I think, are going to be very important areas of research.

TB: So, on this note, I think we should conclude this interview with Dr. Alfred Freedman, one of the pioneers of psychopharmacology in children. Thank you very much, Al, for your contributions to psychopharmacology and dedication to the treatment of the mentally ill and for sharing with us this information.

AF: Well, thank you very much. And particular, thanks for your skillful interviewing technique. I am impressed with the breadth of the material you were able to elicit, while keeping me very comfortable. I give you full marks as an interviewer. I am really very grateful to you.

19. KJELL G. FUXE

TB: We are at the annual meeting of the American College of Neuropsychopharmacology in Hawaii. It is December 8, 2001, and I will be interviewing Professor Kjell Fuxe²¹ from Sweden for the archives of the College. I'm Thomas Ban. We should start from the very beginning, if you could say something about your early interest and education, and then we go on to your professional activities.

KF: I will do my best to summarize my life. It all started in 1938, when I was born in Stockholm on the 25th of April. It was very peaceful in Stockholm in those days but the second world-war, was about to start with the Nazis. Thank heavens I was out of it, growing up in Stockholm, away from the war. I will always be grateful for that. So, I had a good beginning to my life, with a very wonderful Mother who loved me like a Jewish mother and protected me all my youth until I entered the University. I guess, early on, I unconsciously realized that having my home with my mother's love, the safe streets, and the food and milk to fill an empty stomach, I could survive. My interest was only to have a good time. However, when starting school at 7 years of age, I found out that within me I had this thing of wanting to compete. I also felt good about going to the Adolf Fredrik's elementary school because I had to have something to do, being full of energy that has kept me going my entire life. Starting to learn offered a way for me to invest my energy in something that seemed worthwhile. Learning was a way to survive. I probably was not aware of these thoughts at the time, since I was just a boy who liked to study. So, this was life during my first twelve years in school, with the last eight years at Norra Latin, a combined secondary grammar school and senior high school where I got a classic education. It was located in the north part of Stockholm, close to home. I was lucky with that school. It gave me a chance, if I got good marks, to enter the Stockholm University. I never worked as hard as when I was a senior high school scholar in Norra Latin. I was lucky enough to be accepted by the Karolinska Institute, the medical faculty of Stockholm, and my intention at first was to become a doctor. The medical studies began in 1957, and I took my medical bachelor's degree in 1959. Already in 1958, I began to work as an assistant in the Department of Histology at the Karolinska Institute. In fact, histology

²¹ Kjell Fuxe was born in Stockholm, Sweden in 1938. He received medical and scientific training at the Karolinska Institute at the University of Stockholm, where he remained throughout his academic career. He was interviewed in Waikoloa, Hawaii on December 8, 2001.

was my first course and gave me my first contact with science. During these years, from 1958 to 1961, I was trained in histology, histochemistry, and fluorescence microscopy, by Dr. Bengt Fredricsson and Dr. Ove Nilsson, and in biochemistry by Prof. Sune Bergström. As a student with Dr. Ove Nilsson, I began to work on the lipid granules of the uterine epithelium and its hormonal regulation. In this analysis, I was excited by being able to visualize the epithelial cells with the use of fluorescence microscopy, making it possible to understand in a small way their structure, with focus on the lipid granules. Then, in 1962, Professor Nils-Åke Hillarp came from the University of Göteborg to become the chairman of our histology department. I was very grateful that I became his first pupil in Stockholm. So, I switched from the uterus to the brain with the analysis of brain structure and histochemistry since Hillarp brought with him something very fantastic. He gave us this gift, namely the method to demonstrate catecholamines (CA) or serotonin (5-HT) at the cellular level with fluorescence histochemistry, the Falck-Hillarp technique. Suddenly, you could do studies you had only dreamt of. You could study the putative dopamine (DA), noradrenaline (NA), and 5-HT transmitters and their regulation at the cellular level, which was, at this time, revolutionary. I was allowed to select my thesis project, and I chose the brain because in my mind it was just a black box. So, this was the beginning of my life in neuroscience. Carlsson, Falck, and Hillarp had, in 1962, published a supplement in *Acta Physiologica Scandinavica*, on the cellular localization of CA in the hypothalamus and demonstrated, for the first time, their localization in varicose nerve terminals, similar in appearance to the autonomic ground plexus of nerve terminals discovered many years earlier by Hillarp. This was one of his several outstanding contributions to science. It was a sad and highly tragic event for all of his students and for Swedish medical science, when he was struck by a malignant melanoma in 1963, discovered too late for effective treatment. He died in March 1965. He left behind a large number of very young, enthusiastic students at the department, including me, who had looked up at him for being a highly creative and brilliant scientist and a wonderful human being. I believe he would have received the Nobel Prize together with Arvid Carlsson had he stayed alive. It was not easy for Sweden to lose such a scientific giant. However, he left behind his group of young Swedish medical scientists, the so-called amine group, who could continue his work, and build up a new neuroscience tradition in Sweden based on his achievements. The amine group was formed in the histology department after his death in 1965.

I defended my thesis on “Evidence for the existence of central monoamine neurons in the brain,” in April 1965, about one month after his death. My work with Hillarp began with setting up the Falck-Hillarp technique in Stockholm, developed by Bengt Falck and Nils-Åke Hillarp at the department of histology, University of Lund. It was a tough task to set it up since there were variabilities in the reaction of monoamines with formaldehyde gas. Sometimes the reaction was too weak and the monoamines could not be properly detected. Sometimes there was a diffusion of the monoamines and no monoamine localization to cells and their terminals could be observed. Bertil Hamberger, now a professor of surgery at the Karolinska Institute, with other colleagues from the amine group, developed an important method to standardize the formaldehyde fluorescence technique of Falck and Hillarp. He discovered that the water content of the paraformaldehyde powder used was crucial and developed a method with the optimal amount of water in the reaction. This was an important contribution, for which he should be properly acknowledged. It was just a one-page publication in 1965, but a very important page, that had a major impact on the field. In the 1960s, we mapped the major DA, NA, and 5-HT pathways. We discovered the nigro-striatal dopamine system, the meso-limbic dopamine system, and the tubero-infundibular dopamine system. We also contributed to the mapping of the meso-cortical dopamine systems. We mapped the major descending and ascending brainstem NA systems from the pons, mainly locus coeruleus, and the medulla oblongata to the spinal cord and the telencephalon and diencephalon, respectively. We also mapped the brainstem 5-HT systems from the caudal and rostral raphé nuclei with projections to the spinal cord and the telencephalon and diencephalon, respectively. This work was very much a team effort, and I was happy to collaborate with Annica Dahlström, two years younger than me, who is now professor of Neurobiology at the University of Göteborg. We worked well together, in the early years from 1963 to 1965, and had a lot of fun doing so. We also had a nice collaboration with Arvid Carlsson and his group in the 1960s. They helped out very much in the mapping of the monoamine pathways, since they provided the biochemical counterpart. Knut Larsson from the department of psychology at the University of Göteborg made an important contribution by performing lesions of the monoamine systems. Dr. Nils-Erik Anden, in Carlsson’s group, played an especially important role in this collaboration. In 1966, we summed up part of the work in a review article we wrote together. It was based on a lecture I gave, in 1965, in New York, at a symposium on the biochemistry and pharmacology of

the basal ganglia. The proceedings of this meeting, the Second Symposium of the Parkinson Disease Information and Research Center, was edited by E. Costa, L. Cote, and M. Yahr, and published by Raven Press, New York. In 1971, Urban Ungerstedt, now professor of pharmacology at the Karolinska Institute wrote a beautiful thesis on monoamines, based in part on the Falck-Hillarp technique. All these works together represented truly important contributions. I believe it was the dawn of chemical neuroanatomy. The Cajal-Golgi mapping with the silver impregnation technique was followed by transmitter based mapping. I believe this was fundamental, also for neuropsychopharmacology, since pharmacologists could begin to understand better how all these neuropsychotropic drugs acted on the neural circuits of brain and where their primary targets were located. In fact, in the 1960s, we began a fine collaboration with Arvid Carlsson to understand, in a better way, the mechanism of action of the classical antidepressants, like imipramine. With Anden and Hans Corrodi, we gave functional correlates to the postulated DA receptor blocking activity of classical neuroleptics, like haloperidol and chlorpromazine, as pioneered by Carlsson. We elucidated also the mechanism of action of hallucinogens of the indolalkylamine type, like d-LSD, based on the discovery of their ability to act as postjunctional 5-HT receptor agonists, a property that may mediate their hallucinogenic activity. In 1967, with evidence that apomorphine may be a DA receptor agonist, in collaboration with Anden and Corrodi, we began to discover novel dopamine receptor agonists for the treatment of Parkinson's disease. So, there was a world full of neuropsychopharmacology, which interacted with the mapping world, and vice versa, and I was there in both of them.

Our antidepressant work with Arvid Carlsson began in 1965. It showed that classic antidepressant drugs blocked the uptake mechanism for NA in the plasma membrane of the central NA neuron systems but not of the DA neuron systems. In contrast, d-amphetamine, in this analysis, was shown to be a DA and NA releasing drug, which probably mediated its rewarding actions. In this period, I started to believe that we must have an uptake-concentration mechanism for 5-HT in the plasma membrane of the 5-HT neurons, similar to the NA uptake concentration mechanism. Ungerstedt and I could demonstrate, after reserpine depletion of the monoamine stores and intraventricular injections of 5-HT, a nice uptake of 5-HT in the 5-HT terminals. Then, I told Arvid Carlsson about our findings, and we continued our collaboration by analysis of the effects of antidepressants also on the 5-HT uptake. We found that the classical antidepressant drug,

imipramine, had a significant blocking action on the 5-HT uptake concentration mechanism. This was the beginning of the story on the effect of antidepressants on 5-HT neurons with the development of SSRIs.

TB: When did that happen?

KF: The paper on the intraventricular injection of 5-HT was published, in 1967, in the *Journal of Pharmacy and Pharmacology*. The following year, in 1968, in the same journal, Carlsson, I, and Ungerstedt published the first observations that imipramine could block the 5-HT uptake-concentration mechanism in the central 5-HT neurons. In the same, year Corrodi and I could also show, as published again in the *Journal of Pharmacy and Pharmacology*, that imipramine reduced 5-HT turnover in the brain using the tryptophan hydroxylase inhibition method. In 1969, Corrodi and I published a follow up paper with a number of imipramine-like drugs. Thus, our original story was published in these three small papers. They are almost never cited but the first observations are there. The work with Arvid Carlsson was continued with two papers published in the *European Journal of Pharmacology*, in 1969, showing that some antidepressant drugs may preferentially block the 5-HT uptake concentration mechanism in the surface membrane of the central 5-HT neurons, while others may preferentially block the NA uptake concentration mechanism in the surface membrane of the central NA neurons. Arvid Carlsson, together with Hans Corrodi and others at Astra, went on to develop novel compounds with rather selective actions on the 5-HT uptake-concentration mechanism, the most famous one being zimelidine. However, neuropathy developed in a few patients and its clinical development for treatment of depression was stopped. Instead, fluoxetine with the same mechanism of action came along and took over the scene.

TB: So the original observations on 5-HT uptake in the brain were made in the late 1960s?

KF: Yes, our first observations were made in 1967 and 1968.

TB: Fluoxetine was introduced almost 20 years later?

KF: Yes, something like that.

TB: Actually 15 years later?

KF: Yes. It is nice to have been part of this discovery. The neuroleptic work, performed mainly with Anden and Corrodi, was a follow up of Arvid Carlsson's pioneering neurochemical findings in the brain suggesting that neuroleptics may mainly act in schizophrenia by blocking DA

receptors. The evidence for this was obtained in our work, as published in 1966 in *Acta Pharmacologica et Toxicologica*, and in 1970, in the *European Journal of Pharmacology*. We gave further neurochemical evidence, and a functional correlate to Carlsson's pioneering biochemical findings, showing that in fact DA receptor blockade was involved in their actions. Of importance, was our suggestion, in 1970, that the anti-schizophrenic actions importantly involved a blockade of limbic DA receptors, as published in a book on neuroleptics edited by Bobon, Janssen and Bobon. In the period from 1968 to 1974, together with Anden and Corrodi, we also obtained evidence that hallucinogenic drugs of the indolalkylamine type were able to activate postjunctional 5-HT receptors in the brain and the spinal cord, as shown in studies on 5HT turnover and in functional tests. The first paper in this area of research on d-LSD appeared, in 1968, in the *British Journal of Pharmacology*. We wrote a review on the subject, in 1976, in a book with the title *Schizophrenia Today*, edited by D.Kemali, G.Bartholini, and D.Richter. The hypothesis was advanced that activation of certain postjunctional 5-HT receptors in the brain may be responsible for the hallucinogenic effects of these drugs. In contrast, Aghajanian and his group, in the same period, proposed that activation of the 5-HT autoreceptors on the dorsal raphé 5-HT cell bodies was responsible for the hallucinogenic actions of d-LSD type of drugs. A major achievement by our group, working with Anden and Corrodi in the period from 1967 to 1979, was the development of novel dopamine receptor agonists. It began with studies on the DA agonist properties of apomorphine, in 1967, supporting Ernst's work, in 1966 and 1967, followed by the discovery of the DA agonist action of the French compound ET495 (piribedil), in 1971, and of bromocriptine, in 1973, leading to the introduction of these drugs in the treatment of Parkinson's disease, and also to the introduction of dopaminergic ergot derivatives in brain research.

The important functional model in these DA agonist experiments was Ungerstedt's. It showed that unilateral 6-OHDA (6-hydroxydopamine) injections in the medial substantia nigra lead to a dramatic disappearance of striatal DA terminals on the lesioned side, without touching the striatal DA terminals on the unlesioned side. When these rats were treated with DA agonists or L-DOPA, they turned contralaterally to the DA denervated side. The explanation of this lay in the existence of supersensitive striatal DA receptors on the DA denervated side. After treatment with a DA agonist, the DA denervated striatum will become overactivated in comparison to the intact striatum in terms of DA receptor activity. It is this imbalance of DA receptor activity that leads to

an asymmetry in the basal ganglia activation of motor neurons in the brainstem and spinal cord with the appearance of contralateral rotational behavior. Ungerstedt's model was excellent since the number of turns could be easily quantified.

I was interested in bromocriptine since it produced a marked lowering of prolactin secretion; and, based on a large number of neuroendocrine experiments, Fuxe, Hökfelt and Nilsson, formed the hypothesis that the tuberoinfundibular DA neurons were involved in the inhibitory control of prolactin and LH (luteinizing hormone) secretion. Thus, bromocriptine became a new interesting tool in this analysis. I then discovered that bromocriptine reduced DA turnover in the striatum, using the Falck-Hillarp technique together with semiquantitative and quantitative measurements of CA fluorescence that I published, in 1974, with Agnati. The results were also corroborated biochemically by Corrodi. Then we found that bromocriptine produced contralateral rotational behavior in the Ungerstedt model. Thus there was evidence that it was a DA receptor agonist and probably a novel antiparkinson drug. And bromocriptine became an important drug in the treatment of Parkinson's disease (PD). The DA agonist action of the substance also explained its prolactin lowering actions. My old friend and mentor Dr. Menek Goldstein, was also excited about the bromocriptine story and Menek showed its antitremor activity in his monkey model of PD. It was a unique moment in my life when I met Menek, in 1969. We immediately liked each other and became true friends for the rest of his life.

TB: Where did you meet?

KF: It was at the Second International Neurochemistry Meeting in Milan. We had an exciting time there and decided to work together on the continued mapping of the central CA and 5-HT neurons. Menek had developed highly specific antisera against the CA synthesizing enzymes and had made pioneering discoveries on the biochemical properties of the central CA neurons. We truly felt that this could be the beginning of a great novel mapping of the central monoamine neurons using immunohistochemistry and would lead to the introduction of that technique in chemical neuroanatomy. We were happy to be together and took a train-ride to the Stresa region and enjoyed the spectacular beauty of this part of Italy on a warm summer day. We felt very close and our strong friendship and scientific collaboration lasted for almost 30 years, until his death in 1997, leading to large number of interesting publications.

TB: Let me interrupt here and clarify a couple of things. Am I correct to say that you started as a medical student to work in the Department of Histology at the University, and you have stayed in the same Department, as of today?

KF: Yes, that is the way it was and it is an interesting story.

TB: You got first involved with mapping of the monoamines, and then, in the functional aspects of their activity?

KF: Yes, and also the pharmacological aspects.

TB: Would it be correct to say that yours was one of the first major publications on serotonin uptake?

KF: Well it was one of the first, and it was a very significant contribution, based on work I did parallel to mapping. And my second contribution was the discovery of the DA agonist action of bromocriptine.

TB: They were two major lines of research you were involved in beginning?

KF: Yes, it is true.

TB: So, just to clarify again, the serotonin uptake research started in the late 1960s?

KF: Yes.

TB: The dopamine agonist research related to the treatment of Parkinson's was done about the early 1970s?

KF: Yes. This is true for bromocriptine, but the DA agonist story started, in 1966, with the discovery of the DA agonist action of apomorphine by Ernst and Smelik, in 1966, and Anden, Fuxe, and their associates, in 1967.

TB: It took about 20 years until it moved to psychiatry?

KF: Well, zimelidine, a selective 5-HT uptake blocker, was developed by Astra in collaboration with A. Carlsson for the treatment of depression, in the early 1980s. So we are talking about 10-15 years.

TB: When did you become professor?

KF: I became a prosektor of histology in 1968.

TB: What is a prosektor?

KF: Prosektor, today corresponds to a full professorship, but in 1968, it corresponded to an associate professorship. However, it was an important position since it was with tenure and it had

almost the same benefits as a full professorship. My prosector position was converted to a professorship, in 1979. The prosector position had a special significance since it allowed the newly formed amine group to remain at the histology department and work in peace.

TB: Would it be correct to say that all the research you described so far was based on fluorescence techniques?

KF: First it was amine fluorescence, then immunofluorescence. The former is in fact more elegant, since you could demonstrate the cellular localization of the transmitters DA, NA, and 5HT by converting them into fluorescent compounds by condensation with formaldehyde leading to a ring closure followed by a secondary dehydrogenation.

TB: Then you moved from amine fluorescence into immunofluorescence?

KF: Exactly.

TB: When did this take place?

KF: This took place after I had met Menek in Milan, in 1969, and began our unique collaboration. Let me mention that we had a tremendous demand for quantification of amine fluorescence. So, in the early 1970s, Jonsson, Agnati, and I developed quantitative and semiquantitative methods for the evaluation of amine fluorescence.

TB: You mentioned before that you had published several papers with Menek.

KF: The first paper from our work was published, in 1970, on the location of DA beta-hydroxylase in the brain by using immunoreactivity. The good news for me, in the 1970's, was that I got a very important scientist to my laboratory. His name was Luigi Agnati and he became professor of human physiology at the University of Modena some years later. He came to my lab in the early 1970s and stayed for a year. He was an outstanding scientist and became a genuine friend. We have by now, worked together for over 30 years.

TB: Let us move ahead now and tell us about your research in the late 1970s and early 1980s.

KF: In this period, Luigi and I began our fundamental work on receptors leading to the development of the concept of intramembrane receptor-receptor interactions. There were many new peptides discovered and we did not understand how the integration between peptide and monoamine signals took place. We felt that one way could be through direct reciprocal interactions between the peptide and monoamine receptor subtypes in the surface membranes of neurons regulating the affinity and density of the participating receptors. Such direct interactions would be

a fine way to tune receptors and send conditioned receptor signals to the ion channels and enzymes controlling the excitability and metabolic state of the nerve cells. This would be a new fundamental integrative mechanism in the cell, operating at the membrane level. We began the experiments in a small way and had lots of problems. We had to work at least a year before getting any results at all. Finally, we got results in membrane preparations from various brain regions and could observe modulations of the binding characteristics of monoamine receptors by agonist activation of peptide receptors in the membranes. However, the modulation of affinity and density by peptides, e.g., CCK peptides and Substance P, was small, e.g., 20-30% changes of K_D values. No one, except our team, believed that this could have any possible physiological significance. But Luigi and I, with our teams, struggled on. We very much believed in this form of receptor plasticity, involving direct receptor-receptor interactions. Of course, in those early days, we did not know the molecular mechanism bringing the two receptors together. Our first papers appeared in 1980 and 1981. We organized an International Wenner-Gren Center Symposium on receptor-receptor interactions, in 1986, with the proceedings published, in 1987, by Macmillan Press. There were other groups working on receptor-receptor interactions but at the meeting few believed in our story. It did not have an impact at the time. The major thing at the meeting was Greengard's important story on indirect receptor-receptor interactions via intracellular loops causing phosphorylation or dephosphorylation of the receptor. This work did have an impact. However, Luigi and I, with our teams, struggled along leading to the publication of a large number of papers on intramembrane receptor-receptor interactions. In a review paper we published (Zoli et al), we proposed that the direct receptor-receptor interactions were the result of receptor heterodimerization. This was in 1993.

In 1998 and 1999, the breakthrough came when several groups gave experimental evidence of GABA_B receptor heterodimerization. In the year of 2000, we obtained evidence through the collaboration with the Franco team in Barcelona for the existence of functional A₁/D₁ heteromeric receptor complexes that gave the molecular basis for the antagonistic A₁/D₁ receptor-receptor interactions. At the present meeting, I will speak on the antagonistic A₂/D₂ receptor-receptor interactions and their relevance for treatment of Parkinson's disease and schizophrenia. In 1991 and 1992, we proposed the introduction of A_{2A} antagonists in the treatment of Parkinson's disease and in 1994, the use of A_{2A} agonists in the treatment of schizophrenia. We believe that we will

develop many new drugs for neuropsychopharmacology based on the receptor-receptor interactions taking place via the interface of receptor heteromers in the surface membrane. I just would like to mention that in 1982, the Agnati-Fuxe teams published a paper in *Medical Biology*, introducing the hypothesis of “the receptor mosaic hypothesis of the engram.” We postulated that the formation and stabilization of clusters of receptors and mosaics, in the surface membrane with multiple receptor interactions, represented the molecular mechanism for learning and memory. It has been a fully forgotten paper. Now, 20 years later, it seems to be a true story.

TB: Did the work on monoamine receptor interactions start in the late 1970s?

KF: Yes, it began in the late 1970s.

TB: Then, in the 1980s?

KF: Another important story, in the 1980's, was the introduction of the concept of volume transmission (VT), by the Agnati-Fuxe teams. We first published on it, in 1986, in *Acta Physiologica Scandinavica*. We stated that there exists in the CNS, besides the rapid wiring transmission, (WT), with synaptic transmission as the prototype, a slow mode of communication in brain involving the diffusion and convection of transmitters and modulators in the extracellular fluid and CSF. This concept was based on a number of observations, like the detection of spread of CA after their microinjection into the brain, the appearance of diffuse neuropil CA fluorescence after amphetamine treatment, detectable by the Falck-Hillarp technique, the discovery of non-junctional monoamine varicosities in the brain by Descarries and colleagues, and the demonstration of ion diffusion in the extracellular space. The observations of transmitter-receptor mismatches were a major factor for our introduction of the concept of VT. To Agnati and me, it represented the architecture for slow, long distance VT. The best identified signal for long distance VT appears to be Interleukin-1- β , as shown by Jansson and colleagues, in 2000. This is the mode of brain communication mimicked by drugs acting on the brain and therefore of highest relevance for neuropsychopharmacology. Luigi and I are actively pursuing this story of VT vs. WT in the regulation of the cellular and molecular networks of the CNS.

TB: So what would you call your most important contribution, the discovery of receptor-receptor interaction?

KF: Yes, I think so. The receptor-receptor interactions have been the most important contribution made by the Agnati-Fuxe teams. We were 15 years before any other team. But the introduction of the VT concept with evidence for its existence, also by our teams, takes a strong second place.

TB: It seems that at the beginning, the scientific community was skeptical about receptor-receptor interactions, but apparently this is not the case 20 years after.

KF: Yes, it has been a tough battle but the intramembrane receptor-receptor interactions survive over the years. You just have to endure, and if you endure long enough, you finally get a story accepted if it is true. The receptor-receptor interaction story has now been accepted and recognized as a novel principle in molecular neuropsychopharmacology.

TB: Are you a medical doctor?

KF: Yes, but I was never a clinician, with the exception of having had a temporary position as a doctor in the summer in the islands off the northwest of Sweden.

TB: I understand that all through your professional life you did research. What was your first paper on?

KF: It was on preservation of cholinesterase and its histochemical demonstration. It was done with Bengt Fredricsson, my first teacher, Bo Holmstedt, a famous neuropsychopharmacologist, and with Folke Sjöquist, now a famous clinical pharmacologist. The collaboration was again initiated by me, in 1972, to study with Holmstedt the effects of the hallucinogenic compound 5-methoxy-N,N-dimethyltryptamine. That led to a paper on the central monoamine neurons that was published in the *European Journal of Pharmacology*; and work with Folke Sjöquist on the actions of apomorphine on body temperature in the mouse, also led to a publication in the *Journal of Pharmacy and Pharmacology*.

TB: When did you publish your first paper?

KF: This first paper was published in 1960.

TB: What was the last paper that you published?

KF: One of the last papers I published (2001) was related to volume transmission. It was on 5HT terminals and their relationship to the 5-HT_{2A} receptor immunoreactive processes giving structural support for VT in 5-HT neurotransmission. Another recent paper of mine, on mGluR₅/D₂ receptor interactions was just published in *Neuropsychopharmacology*. This was done in collaboration with

the Patrizia Popoli team, in Rome, and is a good example of the ongoing work on receptor-receptor interactions.

TB: You are still very active?

KF: Yes, I think I have never worked as hard as during these last years, with the exception of my school days at Norra Latin.

TB: You started to attend ACNP meetings quite a number of years ago?

KF: Yes, thanks to my old friend Menek Goldstein. He brought me into the ACNP.

TB: Do you remember when, approximately?

KF: I became a member, in 1994, but Menek invited me to participate in ACNP panels in the 1960s and 1970s. The ACNP meeting was in Puerto Rico, at the time, when I was young. I still remember how much I enjoyed the meetings.

TB: Is there anything else you would like to mention?

KF: I would like to just mention the tremendous importance of having had Menek as my mentor and big brother, during a large part of my life. We have had tremendous fun in science and we enjoyed working together. Science was always the focus, because we were both crazy about it. I would also like to state simply that it is vital to have a life also outside of science. I am genuinely grateful to my family, who has not given up on me even though, because of my activities in science, I spent too little time with them.

TB: Are you married and have children?

KF: Yes. I have a wonderful wife, two sons, and a daughter. They are a very crucial part of my life and at the core of my existence.

TB: On this note we should conclude this interview with Professor Kjelle Fuxe from Sweden.

Thank you very much for sharing this information with us.

KF: Thanks

20. DON M. GALLANT

TB: This will be an interview with Don Gallant²² for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the American Psychiatric Association in New Orleans. It is May 7, 2001. I'm Thomas Ban. I think we should start from the beginning: where and when were you born and if you could tell us something about your childhood, education and early interests?

DG: Well, I was born in Brooklyn, New York; I spent my first 17 years going to school in Brooklyn. My family situation was very comfortable. We were middle class. I had one sister. I went to Boys High School in Brooklyn, which was, at that time, considered to be a high school in a relatively dangerous area, Bedford-Stuyvesant, but I never had any problems. After graduating, I went to Tulane University. One of the reasons why I went to Tulane was because a doctor who lived on my block went to Tulane Medical School, and we all respected and loved him very much. So, that was my idea at that time. At Tulane, for some reason, I fell into love with physics, and so, instead of taking a pre-med course, I ended up as a physics-major. In fact, one of my idols was the Chairman of the Department of Physics, Joe Morris. He had worked on the atomic bomb and I was fascinated by him. He had lost several fingers from radiation, and I thought he really was in the forefront of research. He was my hero for a while, and I was thinking about making physics as a career. But later on, my excitement decreased in the area of physics. The bomb had been dropped. The hydrogen bomb was being worked on and I didn't see anything really exciting or rewarding to pursue in that area. The devastating effects of the atom bomb discouraged me. So, I ended up at Tulane Medical School. In my sophomore year, Dr. Robert Heath, who was a former member of the ACNP, talked to the class. He was a charismatic man. He was very impressive, a tall good-looking man. In fact, Time Magazine had a write-up on him. They called him the Gregory Peck of psychiatry. I thought that psychiatry may be a good specialty for me. When my friends heard about that, they were very aggravated. They accused me of leaving medicine. In those days, psychoanalysis dominated American psychiatry; the Brody-Redlich concept of the schizophrenogenic mother. John Rosen wrote a book, "Direct Analysis," dealing with

²² Don M. Gallant was born in Brooklyn, New York in 1929. He received his M.D. degree and completed his residency in psychiatry and neurology at Tulane University, where he spent the majority of his career. He was interviewed in New Orleans, Louisiana on May 7, 2001.

psychoanalysis of schizophrenics. I found all of this hard to accept, but this was the predominant influence in American psychiatry at that time. In fact, in order to progress academically in medical school psychiatry departments, you had to be an analyst at that time. Anyway, I thought I'd spend a summer as an extern in a psychiatric hospital to see if I really enjoyed psychiatry. So, that summer, in my sophomore year, the summer of 1953, I ended up at Gowanda State Hospital, which is a state hospital about 30 miles south of Buffalo, New York. It was a fascinating experience, but also a terrifying experience. I enjoyed the patients. In fact, I had tremendous empathy for them. I really started understanding the severe incapacity of schizophrenia and psychotic depressions. At the same time, the treatment methods were unbelievable, particularly at this hospital.

TB: Tell us something about the different treatments used at the time?

DG: Insulin shock therapy was the main treatment modality that was used. One of the psychiatrists, the medical director of the hospital, came from Austria. He was using insulin shock therapy more than any other modality at that time, and I, as a medical student just finishing my sophomore year, was given the temporary job of injecting 50 percent glucose in a gigantic syringe, with a "horse" needle, and trying to bring patients out of their insulin coma. It was a nerve wracking experience, because what we used was like a "horse" syringe and I had to inject them, intravenously, before they started convulsing. Pushing the 50 percent glucose through the syringe was like pushing molasses through a syringe. And, even to this day, I get nervous when I think about it. At the same time, we saw a number of amphetamine addicts and they so closely resembled paranoid schizophrenia that I just couldn't fathom schizophrenia not being on a molecular or metabolic basis. I mean, they were just qualitatively different and seeing how the amphetamine psychosis so closely resembled the paranoid schizophrenic, I felt that psychoanalysis really was way off track. So, when I came back to Tulane, I definitely committed myself to psychiatry since it was one of the few places with an emphasis on the organic cause of schizophrenia. My empathy for the patients was very intense.

TB: Where did you do your residency?

DG: I stayed at Tulane for one special reason and that was that our department has always had a combined neurology and psychiatry department, right from the very start when Dr. Heath came down here. I felt that schizophrenia was an organic metabolic problem. I wanted to get my feet on the ground, so I actually started off in neurology residency in the first year. I ended up as Chief

Resident, because some of the residents were drafted into the service at that time. So I had a very good experience in neurology, and then, went on to psychiatry. At the same time, Dr. Heath, understanding my interest in pursuing research, asked me to start interviewing some of his patients who had subcortical electrodes. The number of quintuplet electrodes would vary anywhere from 80, up to as many as 120 electrodes, implanted in the hippocampus, the thalamic nuclei, pre-frontal cortex, and the limbic system, of course. I had some fascinating experiences that I can still recall today. I was always interviewing in a blind manner. We had this one-way mirror room and I would sit in the room with a patient. The electrodes were under a cap that covered the patient's head, so when he went out in public, all that showed was a little cap, and no one could see that he was wearing these electrodes. The wires would go through a little hole in the wall of the one-way mirror room and on the other side they did the stimulation. Even though I was blind as to time of stimulation and location, I was able to tell almost every time they stimulated the hippocampus or the amygdala. Now, this was in 1955 and 1956. Psychoanalysis still dominated academia. I remember one déjà vu experience vividly, a patient saying to me, suddenly, "you know, you look exactly like this priest that was in my church back in Baton Rouge, LA," and described the priest exactly just the way I appeared. This, to me, was unbelievably fascinating. One other person I knew, who was also doing this type of work, was Delgado up at Yale. Every time Heath stimulated the amygdala, the patient would become uncomfortable, fearful, or angry at different times, according to the section of the amygdala stimulated. I thought, my God, this is real and it was a fascinating, an incredible experience for a young person not even out of residency. And then, there were fascinating people that used to drop by to visit us, because they had heard of Heath's research, which had been mentioned in Time Magazine. For example, we had this biochemist from Sweden by the name of Ehrensvar, an unbelievably interesting man. He had written a book, "The Biochemical Adaptation of Man," along the same lines as Darwin's theory of evolution; the book was about the theory of biochemical evolution from the earliest species up to mankind. He was interested in everything. He also drank quite a bit, and sometimes, he would have alcohol blackouts. He spent about four months with Dr. Heath. Our lab was on the second floor at the medical school. That was our research area, which stayed open 20 hours a day. Heath used to be in it about 18 hours a day. It was unbelievable the amount of time he spent there. But, one evening when Heath was not there, Dr. Ehrensvar came by and he had been drinking. Now, there was

only one technician on the second floor laboratory area at that time. Ehrensvar started writing formulas and the technician told us about this the next day. He started writing formulas, first on the blackboard. Then, he kept writing the formulas onto the door, onto the next room, all around the second floor. Well, the next day we came there and we saw these formulas and we didn't know what he really intended to do, but we were scared to erase the formulas, as we thought that he may have developed some new concepts. Meanwhile, he was drying out somewhere. So, we kept the formulas on the wall for about a day and a half or two days, trying to figure out what his intentions were. Finally, he shows up about two days later, he looks, and he doesn't remember writing them. It was an alcohol blackout. And, not remembering having done this, he said he just didn't understand what he wrote, so we were finally able to erase it and clean up. The Dean was very disturbed about all of this going on in the research area, as he suspected what had happened. I don't know how much I should tell you about Ehrenswand.

TB: As much as you wish.

DG: I mean he was really unusual. He was a wonderful man. One day, he was down at the French Market, Café Du Monde, having coffee and doughnuts with two of our lab technicians. And, in those days, Café Du Monde used to have these gigantic sugar bowls that they'd chain to the table to keep people from stealing these sugar bowls. Well, Ehrensvar was insulted. He thought that there should be trust and that this was unacceptable to him. So he picked up the sugar bowl, ripped it off the table and ran away. They chased him and caught him. They called the police and they wanted to lock him up, but Dr. Heath intervened and stopped it from happening. He was attracted to Heath's work on Taraxein.

TB: Am I correct that we are towards the end of the 1950s? Could we go a little bit back in time?

DG: Right, right.

TB: It seems to be that Bob Heath had a major impact on your career.

DG: Oh, yes.

TB: Probably, he was the single most important person for you deciding to become a psychiatrist?

DG: I would say, yes.

TB: You attended his lectures as a medical student and started psychiatry before the introduction of the new psychotropic drugs?

DG: Yes.

TB: You talked about insulin coma therapy, and also about seeing amphetamine addicts, who resembled paranoid schizophrenics. Is there anything else you would like to tell us about that period?

DG: Well, actually, I remember one incident when I was extremely embarrassed at Gowanda State Hospital. I haven't thought about this in some time, but there are some incidents that always stay with you. One of our assignments was to work up some of the patients and present them to the staff, and one of the patients I worked up was a man of about 77 or 78 years of age. He had some problems with memory, some problems of orientation, and in addition to having these memory problems, which were primarily organic, he also told me about some delusional material about some oil wells he owned in New York State. Having grown up in Brooklyn, New York, I had never heard of any oil wells in New York State. When I presented him to staff, I presented him as a dementia case, and also mentioned his delusions about the oil wells; and it became part of his diagnosis. Well, about a week later, his son shows up at the hospital, and yes, he had oil wells in New York State. I never got over that. So, I think that was a good lesson. It always made me hold back and not be too impulsive in my evaluations of patients or of people.

That memory, of course, has stayed with me all of these years.

TB: Was this in the early 1950s, about '53?

DG: Right.

TB: Didn't you enter the army after medical school?

DG: No, after residency, I was drafted into the Air Force, and since I had training in neurology and psychiatry, they decided that I could do both. So they sent me over to Clark Air Force Base in the Philippines, which was a base, at that time, of about 25,000 people, including civilians and families associated with the base. In addition, I had to be responsible for treating a lot of US Government employees living in Southeast Asia. I was the only psychiatrist in that area at that time, from 1959 to '61. That was before Vietnam blew up. I was the only psychiatrist for the United States Air Force, Navy, Marines, CIA, ICA, in Southeast Asia, in addition to Clark Air Force Base and Subic Bay. That's a lot of people that I was responsible for. In fact, I had documented and kept my charts because of the tremendous experience that I was offered. I saw close to 1100 patients in two years. At the same time, I had read some of Paul Wender's work with dextroamphetamine in hyperactive attention deficit disorder. This was published about 1958.

We had children in a school on our Air Force base, and a number of these kids, whom I diagnosed as hyperactive attention deficit disorder. I used dextroamphetamine, 5 or 10 milligrams twice a day, and in a number of cases, I had rewarding results for the child, school teacher, and parents. I think that was one of the events that steered me towards psychopharmacology because it was almost like magic. In fact, one of my associations, talking about magic, was my first year of residency at Charity Hospital in 1955. In those days, in Charity Hospital, we had 1800 patients. Alcoholic withdrawal encephalopathy was not unusual because in those days the patients were left lying out in the street for several days and nobody would bring them in. By the time they came in, they were really deteriorated, and in a number of cases, just giving them thiamine, 50 or 100 milligrams intravenously, would eliminate the ataxia and ophthalmoplegia of a Wernicke's Encephalopathy within 30 to 60 minutes, giving me a wonderful sensation of being a doctor, as well as a psychiatrist, and also, making me feel that the medications had a real, definite use. Of course, some of these patients would have residual memory symptoms. It was just amazing how fast the ophthalmoplegia and the ataxia would clear up. It was a tremendous experience. I should mention that we had some excellent faculty. We had Russ Monroe, who went on to become Chairman of the Department of Psychiatry up at the University of Maryland, an excellent clinical person. We had Harold Lief, who went up to Philadelphia to head up the Family Research Unit there at the University of Pennsylvania, and other really outstanding faculty in Neurology. Heath, himself, was boarded both in Neurology and in Psychiatry, as well as having his training in Psychoanalysis at Columbia. Some of our medical students, such as Steve Paul and Peter Rabins, published their first articles under my supervision, and residents such as Chuck O'Brien went on to become outstanding clinical researchers.

TB: Wasn't Heath trained by Sandor Rado?

DG: Yes, yes, he was trained by Rado. In fact, Rado was one of Heath's heroes. At one time, Heath had the fantasy of trying to tie the biochemical concepts of psychiatry with the adaptational theory of psychoanalysis and Rado, of course, was very, very much interested in it. Rado came down a number of times to lecture to us and he was a very impressive man, even though he wasn't that biochemically oriented. He was very impressive in the way he did patient interviews. He had a wonderful touch and just watching him was a learning experience.

TB: So, you knew Sandor Rado?

DG: Yes, a wonderful man.

TB: Can you tell us a little bit more about Bob Heath? No one talks about him any longer.

DG: I know. In fact, I get sort of disenchanted or disappointed, I should say, when I look at some of the current articles in the literature that really evolved out of some of the work that he did. His papers are not even referenced in some of these articles. The neurophysiological and biochemical concepts of dopamine transport and the cerebellum; his organic approach to schizophrenia; and just the basic stuff that we were able to report as far as the various physiologic functions of the hippocampus, amygdala, and the striatum had truly not been reported prior to that time in 1947-1948.

TB: Didn't he start his research in New York at Columbia?

DG: Well, the story is that he had done work on the Columbia Greystone project, which was a project trying to find some other way of treating schizophrenia, neurosurgically, instead of doing frontal lobotomies, which were unbelievably damaging. They were trying to do partial temporal lobectomies. That was part of the Greystone project at that time. He also was well known around Columbia because of his interest both in neurology and psychiatry. He was only about 35 at the time when our Dean at Tulane Medical School was looking to start up the department of psychiatry. We didn't have a department of psychiatry until Heath came down, and this was before I started medical school. It was about 1947, or so, that Dean Lapham asked some people at Columbia if they would recommend anyone who might make a good chairman and they mentioned Bob's name. In the next day or so, the Dean went to Atlantic City. He was lying on the beach next to somebody and started talking about New Orleans and Tulane and mentioned that he was looking for a chairman. The person he was lying next to was Bob Heath. And, that's how Heath came down as chairman of our department of psychiatry and neurology. He came down and said neurology would be under psychiatry, not under medicine, the way it was in other medical schools. So, that was the beginning of our department, at that time. I think he was department chairman longer than almost anybody else in the history of medical schools in this country.

TB: When did he die?

DG: He died last year. He had congestive heart failure. In fact, some of the residents went to interview him about a week or two before he died; put him on tape about his experiences, his memories about the past, and how he became involved in psychiatry and research. I think he also

mentioned one or two funny stories, in fact, about his subcortical electrode patients. The subcortical electrode patients that he selected were either drug refractory epileptics that did not respond well to anticonvulsive medication or severely ill chronic schizophrenic patients that really were not responding at all to treatment. He would do these subcortical electrode implantations with the idea that eventually he would do a temporal lobectomy if they didn't respond to stimulating treatment. Anyway, one of the patients, a temporal lobe epileptic patient, ran away one day, left town, went up to Chicago, to the University of Chicago, Department of Psychiatry. Danny Freedman was Chairman of the Department of Psychiatry, at that time. The patient tried to sell himself for \$5,000, for his hardware, to Danny Freedman. And Freedman, of course, had no idea what was going on. All he saw was somebody in front of him with a cap on his head and he called Dr. Heath and said that he had this patient who is trying to sell himself.

He said, by the way, "Not only do I not want to buy him; I don't have the money, either." And so, he arranged for the patient to be accompanied back to New Orleans at that point. We had a number of interesting experiences. Things were always happening around Heath. He was a very impulsive man at times.

TB: Let me ask you about your early research. Didn't you work, in the 1950's, with hypoglycemic agents?

DG: Yes, right. The idea was to see if you could lower the blood sugar, gradually, and at the same time, see if you can get a therapeutic effect; but that turned out to be totally nil. It was no better than placebo.

TB: Didn't you get involved also in group therapy, in those years?

DG: I became involved in group therapy with alcoholics and drug addicts, who are much more amenable to the group therapy approach. With schizophrenics, I could never really do group therapy. That would only be a ward meeting. It wasn't group therapy.

TB: You also did some research in the '50's with dextroamphetamine, didn't you?

DG: Right. Paul Wender, of course, was the first person who published on its use in ADHD. That was in the *American Journal of Psychiatry*, in about 1956 or '57, right before I went to the Philippines.

TB: Wasn't that your first paper?

DG: Right, that was my first publication, and it was in an *Air Force Medical Journal*.

TB: What did you find with dextroamphetamine?

DG: Well, we had excellent results. The attention span increased; hyperactivity decreased. I did only take classical cases of ADHD and I had about 4 or 5 of them. It wasn't a large study, but it was a very impressive response, that made me realize that psychopharmacology, even on that relatively primitive basis, would be very promising, as far as helping patients.

TB: Are you board certified in both, psychiatry and neurology?

DG: I was board-eligible in both specialties, but I only certified in psychiatry. After taking my psychiatry certification, I just didn't want to go through the testing again, memorizing, and so forth, but I felt that having neurology first helped me get my feet on the ground. In fact, when medical students ask me, nowadays, about going into psychiatry, I usually recommend a year in neurology, to deal with the structure, before they get into something more subjective. My experiences in the Air Force, having such a large number of patients, again, it was really good for me. By the time I left the Air Force, I felt that I had more clinical experience in two years than I would have had in a clinical practice here in the states in four or five years or more. So, I was very fortunate, and also, I was involved in different things. I don't know if you want to go into it, but we had a fellow by the name of McCann, a prisoner of the Communist Chinese. He was supposedly a second hand car salesman in Shanghai, China, and when the Communist Chinese took over in 1949, they couldn't figure out what a Caucasian car salesman was doing in Shanghai, China. They locked him up when they realized he was a CIA agent. He was still in prison by 1959. His wife heard that he had lung cancer, so she appealed to Mao, at that point, on a hardship basis, to see if he would release McCann; and he finally said yes, if we would come and get him. Well, I was the only psychiatrist in that area, so they sent me and the Colonel of our hospital, Colonel Gehring, to Hong Kong. I had some peculiar experiences there, to give you an idea of the CIA. This was in 1959, or so, and I remember some CIA agents in Hong Kong wanted to keep it a secret what we were doing, so they arranged for me to meet them in a bar, in some very poor Chinese area. There were no Caucasians in that section of Hong Kong, and I didn't have anything to wear but an Air Force uniform, no civilian clothes which would stand out less in this little bar. So, I would be meeting with them, wearing my Air Force uniform in secrecy, supposedly, and they'd say, well, McCann is coming tomorrow. Then, the next day, the Hong Kong newspapers would say, McCann is not due till Thursday. Sure enough, the newspapers were right. The CIA was

wrong. This went on for about 3 days. Finally, he showed up at the border on Thursday. I was sent there to see if he was brainwashed. Well, the poor man wasn't brainwashed. But he did have lung cancer, which metastasized to the brain. But, his wife felt comfortable afterwards, since he died on what was considered to be US soil, at that time, rather than dying in a Communist prison cell. I had a number of experiences like that, being the only psychiatrist in that area, as well as the only neurologist at that time. And it was very, very interesting.

TB: What did you do when you came back from the Philippines?

DG: I started off with a psychopharmacology research grant. Bob Felix, who was head of NIH at that time, had selected Jonathan Cole to head up the psychopharmacology research branch and they had this funding for about 19 or 20 ECDEU centers. I think Jonathan Cole was actually looking for people to apply and he called up Bob Heath, realizing that Bob was interested in the organic aspects of psychiatry. Bob applied with Mel Bishop. Now, Mel Bishop was a psychologist that I thought was tremendously, talented. He was really an excellent person. And, Heath wrote up the grant. Now, by the time I came back, the grant had been accepted, and Bob then called Jon Cole to see if he would put my name as the principal investigator. Jon Cole really took a chance on me, because I'd just had a couple of publications from the Air Force. I really felt that I owed a great deal to Jonathan Cole because of his taking a chance on me. He allowed me to be the principal investigator and Mel Bishop the co-principal, at that point. I learned a lot of statistics from Mel Bishop. If it weren't for him, I wouldn't have known anything about statistics. I still know nothing, but I know a little bit of nothing, rather than absolutely nothing. And, Mel was of tremendous help; we worked very well together for many years. In fact, Mel is responsible for one of my most positive memories concerning a compliment made to me at an

ACNP meeting. Correct me if I'm wrong, but it was in January of 1964, even though it should have been in December, but I think it was January at that time, when they had the first meetings. Joe Zubin was a psychologist, a superior psychologist at NYU, very well respected. And, at that time, we didn't have the psychiatric rating scales standardized, quite yet. We were just starting to use the BPRS at the time. So, we used the Tulane Test Battery, which had a lot of statistical evaluations, and I presented the Tulane Test Battery that we used for evaluating our schizophrenic patients and their response to medication. I presented our data having relied upon Mel Bishop's educating me. At the end of my presentation, Joe Zubin came up to me and complimented me on

the presentation and he said, it's nice to see that Tulane has a good psychologist down there. I said, I'm not a psychologist. I'm a psychiatrist. And, he was surprised. And, at that point, I felt that I could not have had the greatest compliment in the world from someone like Joe Zubin, who thought I was a psychologist. So, I still remember that.

TB: Can you tell us something about the Tulane Test Battery?

DG: Well, it was very, very primitive, very simple. Mel extracted some data from one of our simple organic mental status exams. He quantified these data. He also had about 8 or 10 questions dealing with psychoses, that we threw in there. He took the WAIS scale, the eye-hand coordination part of the test, and the IQ part of the test and incorporated them as part of the scoring of the Test Battery.

TB: In what kind of patient populations did you use the Battery?

DG: We had several different patient populations. We had an outpatient population at Charity Hospital, in New Orleans, where we ran a psychiatry service with LSU Medical School, but Tulane was more involved with patients in the state program. It was almost along the lines of UCLA and USC, where USC was more involved in the state program. UCLA had more private psychiatric services going on. The same thing with us; we were more involved in the state program, even though we were a private Medical School. So, I was running this schizophrenic research unit at East Louisiana State Hospital up in Jackson, Louisiana. It was a building that had been given to us by the state. Bob Heath was a very good politician when it came to Louisiana politics and we had 120 patients, 60 male and 60 female patients, and these patients were evaluated for transfer to our research unit. Now, these patients were unbelievably severely chronic. Their mean duration of hospitalization was about 22 years, with a standard deviation of only about 4 years. They had really not been treated by anyone. They had just been warehoused before they came onto our unit, because East Louisiana State Hospital, in those days, was really out in the woods, totally isolated, about 115 miles from New Orleans, with no good roads going up there. I used to have to go there twice a week and it took me about two and a half hours each way, five hours of travel each time. So, this population, when we did some quantitative scoring on organic testing, they, of course, resembled dementia patients. In some data on organic testing, they were closer to dementia than to our acute schizophrenic patients. We had some data along those lines, at that time, but we never really got around to publishing them. The families had given up on these patients; they would

never visit, even though we tried to contact them. So, we tried to get telephone consents from the families to include these patients in our studies. In addition, every study had to have judicial consent. So, the test battery had to be a primitive one for that type of population. In fact, when the BPRS was standardized by Overall and Gorham, we could not use the BPRS the way it was standardized for acute schizophrenic populations. We had to modify it, because on a lot of items, we could not base the score on the response of the patients. So we changed these items to observation items. We used the same scale, but we modified it for that population, while we used the original BPRS for our acute schizophrenic population, which was at the hospital in Mandeville, Louisiana. I also had my alcoholic and drug abuse population at Mandeville. So, we had these four different populations for psychopharmacology studies, and thus, I was involved in quite a few studies at one time with Mel Bishop, of course. Without him, I could never have functioned. In fact, we were so busy, so preoccupied, so involved that I looked up one day and we had published about 25 papers after just two years. I guess that's what helped me to be admitted to the ACNP at that point, in 1963. I don't think I would have ever been admitted to the ACNP now. But in '63, there were fewer people applying, and I had these 25 publications, which was fairly good as far as psychopharmacology was concerned.

TB: Was the research supported by your ECDEU your primary activity in those years? DG: No, I had several primary activities. Looking back now, I think they should have locked me up. I was unbelievably hyperactive at that time, and with someone like Mel Bishop, who was so productive, the both of us were really overdoing things. I would start off my days at about 3:30 in the morning. I would go up to Jackson, do my research evaluations. I used to like to get there before my staff, my daytime staff and my research staff. I never had to criticize them. They just made it their business to come in on time, because I was waiting there for them. It was the best method, I ever found, dealing with staff, to be there before them. By doing that, if they come late or start goofing off, it becomes very apparent to me and to them. Then, after I had done my evaluations in the morning, I would drive to my alcohol and drug abuse center at Mandeville for the afternoon to do my evaluations there. In addition, I was the only psychiatrist treating alcohol and drug abusers in southern Louisiana for the state. Of course, this was a state consultant job. At Mandeville, I had a 32-bed unit that I ran by myself at the alcohol and drug abuse center, with a good nursing staff. After my work at that unit, I drove back to Tulane Medical School to catch up on my

correspondence. Later on, I also became medical director of student education at Tulane, as a third job. So, I would get home by about 6:30-7:00 in the evening, write my research papers, spent insufficient time with my family; got to bed by 11:00 o'clock or so, and, then, I'd get up at 3:30. This went on for years, and that is why I say they should have locked me up. But, I was enjoying it. I realize I was very fortunate to go into psychiatry, and I think I was just lucky to stumble into it the way I did. To have the opportunity to do patient care at the same time on the alcohol and drug abuse unit was fascinating. I ran the alcohol and drug abuse clinic here in New Orleans. In fact, I did quite a few clinical studies in alcohol and drug abuse patients, as well as in schizophrenic patients. I did also clinical studies in outpatients with anxiety and depression in the population at the Charity Hospital.

TB: Those were obviously very productive years. Could you tell us a little more about your research related to ECDEU?

DG: Jon Cole was the heart and soul of ECDEU. I mean, if he had not been given that job, it would have fallen flat. He was so enthusiastic and so pleasant and easy to deal with. We had a bunch of characters, each one of us representing different early clinical drug evaluation units, and we presented our findings, argued, and agreed or disagreed. I'll never forget that one time, in 1962; we had received a drug from Janssen, called trifluoperidol. I should say that our chronic schizophrenic population had almost no placebo response. I mean, we did about four or five double blind studies, in 1961 and '62, and we never had more than a ten percent placebo response in that population.

TB: Didn't you publish on that work.

DG: Yes, we did. You have a better memory than I do. We did publish on that. I think it was in the Archives. Anyway, I only had 12 patients on trifluoperidol the first time. I presented our data at the ECDU meeting, and one or two of the other investigators, who were somewhat older than me, criticized me for sticking my neck out when I was saying that this was a new active therapeutic drug, and not one of those "me, too" drugs. So, a couple of people criticized me for going overboard. Apparently, somebody up at NYU had an acute schizophrenic population and they couldn't really see a difference between the drug and placebo. So, they also disagreed. I felt pretty shaken about it. We went ahead and did the double blind study, and sure enough, trifluoperidol was really a good antipsychotic. I believe that later on, it showed some pancreatic problems in mice,

something along those lines. It never became commercially available in this country. But, of course, that was the first butyrophenone of Janssen we studied. Paul Janssen, in fact, wrote me a very nice letter thanking me for sticking to my guns. Obviously, it helped them. That was just one of the experiences I had with ECDEU. The group, itself, really functioned very well, I thought. It was a group that traded experiences, traded information, traded data, and I think all of us grew from that experience. Going back, I really believe that without Jon Cole, I don't think it would have evolved so well.

TB: Would you like to mention a few people who were involved in the ECDEU program in those years?

DG: Oh yes, trusting my memory, George Simpson, of course, and actually, you and Heinz Lehmann. And then, Herman Denbar, I remember very well. Sidney Merlis and also Sidney Malitz from Columbia were there. I can't remember anybody from the west coast. So it was all people from the northeast, and then, our unit in the south.

TB: Was your unit one of the first units in the ECDEU network?

DG: Yes, I think it was one of the first units. Originally, the grant was directed totally towards schizophrenia, but we opened it up with my alcohol and drug abuse population in Mandeville and depression/anxiety studies at Charity Hospital in New Orleans. We dried out our alcoholic inpatient population for four weeks, or so, and then, did anxiety studies in those who had residual anxiety still persisting after a full four weeks of drying out. These were double blind studies. In one study we did in 1969, we compared doxepin vs. diazepam vs. placebo; doxepin came out looking just as good as diazepam for its anxiolytic effect and we published that in the *Journal of Psychopharmacology*. At first, other investigators didn't pay any attention to these findings. I didn't want to use benzodiazepines in the alcoholic population, who did have a tendency to misuse those drugs. So, from that point on, I was using tricyclics, and later on, SSRI's for decreasing anxiety in generalized anxiety disorders, rather than the benzodiazepines. That was in 1969. Later on, I think in 1990, *Lancet* published an article on the anxiolytic properties of doxepin. So, for many years, I was disappointed that other people had not started using the tricyclics for anxiety.

TB: Well, we also studied the effect of doxepin in anxiety disorders in the 1970s.

DG: Oh, you did?

TB: Yes, we did. In fact, we developed with Heinz Lehmann a conflict tolerance test and doxepin increased conflict tolerance as benzodiazepines did. Can you mention a few other drugs that you studied in those years?

DG: Well, haloperidol, of course. A lot of people were involved in haloperidol at the same time we were. In fact, there was a separate haloperidol meeting that went on in Miami. I remember we were all reporting about the same results: that it was an excellent new drug, the side-effects were minimal to moderate, and that sedation was practically lacking. So it was a much more comfortable drug than chlorpromazine. Molindone was another drug that was interesting for us to study, and then, butaperazine, but nothing much came of that. That was an antipsychotic.

TB: Didn't you work also with mesoridazine?

DG: Oh yes, actually, that was a bad situation. I don't know if you're aware of the story, but in about 1970 or '72, we worked with mesoridazine. Two problems with that were: granulocytopenia that was reported in the literature and we were able to confirm; the other one was the prolongation of the QT_c interval which we found in a double blinded study. I was concerned about that. We conducted a double blind study with thioridazine after that against thiothixene and placebo; and we used a control group of my attendants on the research unit. And, lo and behold, only one of the 13 thiothixene patients had prolongation of the QT_c, and one out of 13 attendants had prolongation after 8 weeks. But 13 out of 13 patients on thioridazine (Mellaril) 800 milligrams a day and 7 of 13 on 400 milligrams/day had prolongation of the Q-T interval. I still remember this. At 400 milligrams/day 7 of 13 thioridazine patients had prolongation of the Q-T interval. We published that. In fact, the cardiology fellow that read the EKG's could identify thioridazine in a blinded fashion. He did this with George Simpson's patients, also. George was fascinated. Well, after we published, somebody from Sandoz called me up and started yelling on the phone at me, criticizing me, saying I was unethical for publishing these data. This was 1972, and I was shocked that someone from a pharmaceutical firm would start telling me I'm unethical for publishing these types of findings, which were unbelievably solid findings. They were controlled double blind studies. They were read blind and, at that point, I never thought that anyone from Sandoz would call me up and say I was unethical for publishing this type of objective data. This wasn't just an opinion. These were double blind studies. The EKG's were read blind and the cardiologist reading the EKG's did not know to what drug group the patient belonged or whether it was a control.

George Simpson sent us the EKG data from his study for my cardiologist to read, and he said that he found the same thing in George Simpson's patients. So, you know, it was solid, solid data and Sandoz Company never made any mention about it. It was published, and nobody paid much attention to it in the literature. It was in the American Journal of Psychiatry, I think. And, now, I think, in the last few years, they have been talking about the study again, but the data has been out there for 20 or 30 years.

TB: Cardiac conductance changes with thioridazine, structurally closely related to mesoridazine, were first reported in the early 1960's.

DG: Early 1960's?

TB: Yes. Three patients died in Kingston, Canada while treated with thioridazine, and it was attributed to cardiac conductance changes caused by the drug.

DG: Sudden death.

TB: Sandoz became interested, at the time, in the effects of thioridazine on the EKG; and in a crossover study with trifluoperazine and chlorpromazine, we showed and published in '63, that it produces prolongation of the QT interval. Lew Gottschalk had similar findings, a little bit later, and he tried to identify the metabolites responsible for the cardiac changes. For many years these findings were dismissed. Now, there is a warning.

DG: That's the only time I ever had somebody call me up and start telling me I was unethical, and the first time I had somebody from a pharmaceutical firm try to prevent publication. It's instilled in my memory.

TB: Didn't you subsequently study the effects of several psychotropic drugs on the EKG?

DG: Oh yes, we did it routinely at the very beginning. You know, actually, we did that with the tricyclics. We saw a few changes. The type of studies that we did would vary from East Louisiana State Hospital in Jackson to Southeast Louisiana State Hospital in Mandeville to Charity Hospital in New Orleans. They were very different types of studies. When it came to selecting patients for the East Louisiana State Hospital research unit in Jackson, LA, there was a problem. The state was segregated, at that time. Patients in the state hospitals were segregated, so we had a choice. Either we were going to transfer Caucasian patients to our research unit or transfer black patients to the research unit. Well, with a federal grant, even though Louisiana was segregated, the federal government wasn't segregated. So with a federal grant, we decided that we better just do our

research on white patients. Thus, our schizophrenic research unit was all white, all Caucasian. It was a paradox, in a sense. Here you have a segregated society and we're doing research on the Caucasians, who aren't in favor of integration. We were able to have both groups of patients, both blacks and whites, at Charity Hospital, but in separate clinics. In fact, we saw differences in placebo response, which we were very afraid to publish, at that point, for fear that people might think we were prejudiced against blacks. We had a white clinic and a black clinic. We had no control over that state-imposed system. We had to do it that way or else be arrested. And, at one time, we did a double blind study of a compound, called JB8181 (desipramine), in a double blind study vs. placebo in the white clinic and another in the black clinic, about 20 to 30 patients in each group. Now, the black and white populations in Charity Hospital, this is 1963 or so, differed significantly, personality-wise. In those days, Charity Hospital was called Mother Charity, and it served the entire population that was poor. The black patients had a positive identification at that time for Charity. The whites, who were at Charity Hospital, were there because they couldn't afford private treatment, and they were much more negative about being in Charity Hospital. These two populations had a significant difference in placebo response at Charity Hospital. In the desipramine vs. placebo study in our white population, we saw a significant drug-placebo difference, but in our black population, because of the significant placebo response, it was about 55 percent, we could see no significant difference between drug and placebo. So, when we added up the data, we saw only a slight difference of drug favoring placebo. Were it not for that segregation, we would have never been positive about the antidepressant properties of desipramine. So we had peculiar clinical drug experiences during that period of time. It was a very unusual time for New Orleans and the state, and we were sort of caught in the middle in the way we were doing research.

TB: So, you had been involved in studying antidepressants as well from the very beginning?

DG: Oh yes. We had some compounds that were serotonin antagonists that we tried out in our population but didn't get any really good positive results using them. At one time, we collaborated with Leo Hollister on a protein fractionation serum project. Heath was interested in that area and Leo was interested a little bit in that area, so we collaborated on our patient populations, but, again, we saw no significant difference between our controls and our schizophrenics. We reported those findings because I felt it was important to report on negative results, as well as positive. Except

for the Sandoz incident, we never had any unusual pressure from pharmaceutical firms. With the present terrible conflict of interest by pharmaceutical firms and investigators, I do believe that bringing back the government financed ECDEU units would help to clear the air. I would say that when I reflect back on these different populations, I feel the most interesting was the significant differences between our acute schizophrenics and our chronic schizophrenics. We called them Type 1 and Type 2 schizophrenics, according to Crowe. Also, we reported on some of the dual diagnosis problems in our alcohol and drug abuse populations. Depression in our alcoholics, of course, was much higher than it was in our nonalcoholic population. So, they were a very good population for doing antidepressant studies.

TB: In the early years, you collaborated with Heath, didn't you? When did you stop working with him?

DG: I reached a point with Heath when I was not able to really collaborate with him after about 1964 or '65. We had a difficult incident, a sort of inappropriate type of situation, inappropriate behavior. He accused me of stealing his research, in which I had no interest. And after that, I told him that it was sad that I could stay at Tulane only if we just did our own separate work. This incident occurred over a patient with diabetes insipidus, of all things. We had a patient in the VA Hospital and one patient at Charity. Both had lesions in the mid brain area. One patient had a temporal lobe tumor associated with diabetes insipidus and the other patient had multiple small infarcts. I was accumulating the data for a joint publication, with Heath as the lead author. I was still a young faculty person. He had been my teacher in medical school, my mentor in residency, and I took it for granted that he would be the lead author on this paper, which really wasn't covering a lot of territory on diabetes insipidus. It was not that important to psychiatry, but he blew up at me, thinking that I was going to take the credit for the paper. It was a very inappropriate, bad scene. So, I couldn't work with him, again. In that sense, he was a little bit overly suspicious. Russ Monroe and Harold Lief both left after some years of difficulty with Bob Heath. I should say that at other times, it was fine and easy to get along with him. At other times, he wasn't that easy.

TB: But you did publish several papers with him before you parted.

DG: Well, he believed that the area, somewhat anterior between the limbic and the prefrontal cortex, was the key area for schizophrenia, and he was focused in that area. He would see

occasional spiking in schizophrenic patients with subcortical electrodes from that area, which he didn't obtain from the temporal lobe region. That was interesting and he published these data. We did the antibody study, the protein fractionation study. But outside of those studies, there was very little. And, I felt bad about it, but it's amazing the way we both functioned separately after '65 and were friendly outside of the investigational work. We got along quite well. It was almost as if he forgot about the incident, that he blew up, and to him it was over. I never forgot the incident, obviously and to me, it was never completely over. I think I'm being a little bit too honest. I was very hurt for a long period of time after that, but I always defended him in public. People both admired and respected him for what he was doing, or else, they thought he was untrustworthy and didn't trust his data. He did have one large research problem, which was "controls." He would not pay enough attention to having good controls for his studies. Talking about controls, there was an incident concerning Heinz Lehmann. Heinz Lehmann, who I considered to be a very gracious, friendly, open person, came down as part of a site visit to look at Heath's work. On our research unit, Heath grabbed him, and before Lehmann knew what was happening, Heath had blood being drawn, using Lehmann as a control. And, he didn't even object. Later on, when it came to evaluating Heath's Taraxein work, almost everybody was totally negative about it. But Lehmann sort of held back for a while and said, well, give him a chance. I think you know Lehmann, of course, much better than I ever knew him, but I think that's the way he was. That was a terrible joke, but Heath would do things like this. He was very impulsive.

TB: Could you tell us more about your research related to ECDEU? You were involved with ECDEU for well over a decade.

DG: Sixteen or 17 years, something like that.

TB: It was a very, very productive period in your life.

DG: Yes, actually, there was an interesting thing about being productive and receiving ECDEU support. Actually, belonging to ECDEU gave us grant support, not for just doing the drug studies, but also to support my base salary at Tulane. So it enabled me to do a lot of work outside of ECDEU. It was of fantastic help to me in all areas of my clinical experiences, not just in the drug studies. Within the ECDEU formula, itself, I think it produced quite a few outstanding people, Arnold Friedhoff, Sam Gershon, Sid Malitz, Max Fink, who were very good. So, it was very rewarding and stimulating, very good people, for the most part. The ECDEU also permitted us to

do our anti-anxiety studies and our antidepressant studies. In fact, we even did a study with metronidazole in alcoholics that was a “spin off” from our ECDEU grant

TB: Tell us something about your findings with metronidazole in alcoholics?

DG: Well, this was interesting. We did a double blind study vs. placebo and we found no difference. It was a 6 month study. At the end of the 6 months, we found no difference in the abstinence rate or the number of drinking days. So, even though, theoretically, metronidazole might inhibit ethanol to some extent, it didn't perform clinically in the area of alcoholism. Until that time, there weren't too many controlled research studies in the psychopharmacologic aspects of alcoholism. In fact, these protocols led to some comparison clinical studies with “criminal alcoholics” with good results. I was disappointed that our data was not utilized by other substance abuse investigators. Our data is even important for the present time. What we meant by “criminal alcoholics” were patients coming out of our state penitentiary in Angola, which is a pretty bad state penitentiary; back in 1969, it was a horrible state penitentiary. These patients had committed major crimes, such as homicide, rape, armed robbery, directly or indirectly associated with alcohol problems. They were randomly distributed into two groups. One group was compulsory treatment. This was a small study, only about 24 patients. One group had to come regularly every week to the clinic for treatment and take Antabuse (disulfiram). Now, these were early release people. If they wanted to get involved in the project, they were given early release. Otherwise, they had to serve their regular time, so it was free choice. If they chose early release, then they were randomly assigned, one group to come to us for at least 6 months, in addition to taking Antabuse. We needed the 6 months to work out their initial anger about the enforcement of treatment. And the other group had to come to our clinic only once, in addition to the regular parole, and then, we had to talk them into coming on a voluntary basis. At the end of one year, even though it was small study, the results were significantly different. In the voluntary group, only one out of 12 patients was doing okay. Of these 12 patients, 9 of them were back in jail at the time of the follow-up at one year, and 2 of them were at large out of state for breaking parole. However, in the compulsory treatment group, about 7 or 8 out of the 11 or 12 were doing well. So, although it was a small study, it really told us something. If you have enough of a hammer to hang over the “criminal alcoholic” and probably the “criminal drug addict,” and the compulsory treatment is long enough to work out the anger about being forced to get treatment, then this

approach can be very worthwhile. This data was published in 1969, and nobody ever really took advantage of that data that I know of, until recently. New York State is now involved in this type of project, but it was disappointing that people did not take it up in the 1960's. We did some other similar projects along these lines. Remember Sam Guze? He was chairman of the Department of Psychiatry at Washington University Medical School in St. Louis. He was an excellent person. He did some research on crime and poverty and was responsible for getting the "revolving door alcoholic" grant. I was running a free clinic at the Fischer Project, which was a low-income housing project in New Orleans, at that time. I worked there Friday afternoons and all day Saturdays.

TB: You became very much involved in the Fischer project, didn't you?

DG: Right. This Fischer Project had no methadone clinic, no medical clinic, nothing, so I started a general medical clinic. Sam Guze published an article; I think it was in the Archives, I'm not sure, on people from the poverty area in St. Louis, a black project area, who ended up in jail. What he reported was, if a child missed 10 days in a row at school in the first grade in one quarter, and missed 10 days in a row at school in one quarter of the second grade, he or she was twice as likely to end up in jail as somebody who had not had that type of absentee attendance; just those two pieces of data, he reported. So, having spare time on my hands, we hired an African-American woman, who had a car, and paid her about \$30.00 a week. We also had contact with the school principal in the Treme area here in New Orleans, who gave us the attendance records of these students. If a kid missed 10 days of school in a row in the first grade and 10 days of school in a row in the second grade, we had the woman start picking up the kids and bringing them to school in her car. Now, it was amazing the way their grades improved in six weeks, fascinating, just by coming to school regularly. In fact, to show you how important that small piece of data is, there were two little girls that missed about 20 days of school in a row in the first grade and about 20 days of school in a row in one quarter of the second grade, and by the time our lady went to pick them up, we learned that their father had committed suicide the previous week. The wife had died from cancer the year before, and he was deeply depressed that year and a half, not paying attention to the children. They were running wild. Missing school in those two pieces of time, usually meant that there was a tremendously fragmented home situation that had to be adjusted immediately. So, that was spin-off from the time that was allowed to me for having my base salary supported by the

ECDEU grant. We were doing our obligated research work, but also doing “spin off” work at the same time. At the Fischer Project, we were paying for our patients’ methadone; the heroin addicts had to come over from the west bank on the other side of the Mississippi River, to the east bank to get their methadone every day. I don’t know if I ever mentioned this to you in one of our meetings. Of course, it was an interesting, but sad thing.

TB: Could you elaborate further on this?

DG: The clinic was a general medical clinic. Thus, we made contact with the population to get them to realize that we were not out just to do research with them. We also used that population to teach my medical students about delivering medical care in poverty areas. If the patients came to the methadone clinic on a regular basis and stayed clean for two months, we would get them a job. If they stayed on the job for three months, which meant that they were clean for five months, we would pay for their expenses to move out of the projects. When they reached that point, most of them would not want to leave the projects. That was one of the saddest discoveries I ever had. They were too scared to move out of the projects. It was their comfortable cocoon. They’d been there too long, and thus, they’d wanted to stay there for the rest of their lives. That’s where all the shooting up of IV injections and the selling of drugs was going on, in the Fischer Project. So I felt a little bit disenchanted by my experience after four years, or so, and realized that we came to these people too late in the course of their illness.

They just couldn’t make it socially outside that environment. So, that was a very depressing experience, to say the least. I undertook all of these clinical experiences for my own learning.

For teaching, this was very, very important; still is important to me now.

TB: Weren’t you the director of education in the department?

DG: Yes, right.

TB: From the early 1960’s?

DG: No, later on. I became Director of Medical School teaching in psychiatry in the late 1970’s or early 1980’s. The previous director had left and they had nobody to take over. I enjoyed medical school teaching and I had some positive reward out of it. I call it “selfishselflessness.” They had what they call The Owl Club at Tulane; if you’re an outstanding teacher, you’d get an award every year. I had been getting this award every year for 15 years, or so, and in fact, the graduating class gave me an outstanding award for medical student teaching. That positive

feedback, of course, is essential if you're going to really keep functioning and enjoying what you're doing. Being the Director of Medical School Education in Psychiatry was a real challenge, of course. To get full time faculty to really put the hours of teaching in became more and more difficult, because those people who did not have grants to support their base salaries would have to either see private patients or do consultation work with outside institutions. It became very difficult getting people to volunteer to do teaching. And sometimes, I felt like a total bully, trying to get them to spend an extra hour or two a week. It was rewarding, but also frustrating. Nowadays, it's still a problem, and the present director of medical school education in psychiatry still has problems in getting people to give more lectures since it takes them away from their income, much more so than it did, say, back in the years when we were still in the 1960's and the '70's; we had federal grants to back us up and the grants were easy to get in those days. So, when old people like me come down here to do some teaching, they're very grateful. I mean, because I'm helping them to have extra hours to support their income.

TB: So you had grants for teaching. But you also had other grant support for some of your other projects.

DG: Well, we had the grant to do the compulsory treatment study with alcoholics. In fact, we did another one after the criminal alcoholic study. We did a "revolving door" alcoholic municipal study. That was federal grant support.

TB: When was that, approximately?

DG: It was about 1972. The criminal alcoholic study was in 1969. So, we thought that maybe compulsory treatment might also work for the "revolving door" alcoholics. Now, there is a difference between these populations. The revolving door alcoholic or the skid row alcoholic is less dangerous to the community than the criminal alcoholic, but we found out he's less treatable. This was a large 100 patient study which was funded by a separate grant. We had 50 patients come to our inpatient program for four or five week treatment, and then, got them a job and paid for a place to stay. That was our compulsory treatment group. If they missed a clinic visit, they went back and served the remainder of their sentence, which was usually between 60 and 90 days in Parish Prison, a totally different type of club to hold over someone's head, compared to Angola State Penitentiary for the "criminal alcoholics." The voluntary group just had to come to us once a week in the clinic, and if they decided not to come, they were dropped.

We did extensive follow up. Now, doing follow up on “skid row” alcoholics is not easy, because they move around a lot; although, in New Orleans, they liked the climate, so many of them stayed here. But they still moved around a lot. So, we hired someone who had some detective skills to locate our patients for follow up: in Arizona prisons, everywhere, using telephone books, school systems, or what not. Anyway, he was able to locate, it sounds impossible, more than 80 percent of our patients in a one year follow up, but it turns out the compulsory treatment for this group was a total waste of time, compared to the “criminal alcoholic” group. There were real differences. This group had nothing to lose. They had already been arrested an average of 50 times or more. Now, we had one person, named “Whitey,” who been arrested close to a thousand times. I know that sounds impossible, but it’s true. Of course, what he would do when he needed a place to stay, he would call the police and tell them there’s a drunk lying in the street and they should pick him up because he’s blocking the store entrance. Then he would lie down in the street. They’d come, pick him up, and take him into Parish Prison, where the food was pretty good in those years. We had a psychiatric evaluation profile, the PEP. Jerry Levine originated this, by the way. He standardized this psychiatric evaluation profile. It has a factor in it that is “overly optimistic.” These “skid row” patients scored significantly higher on the “overly optimistic” scale compared to our “criminal alcoholics.” They thought, “I’m going to make it”; “I can do it”; “no problem”; “I’m off alcohol the rest of my life”; this type of unrealistic approach was one factor. Another factor was “self-esteem.” They scored very low on “self-esteem.” So this combination of very “low self-esteem,” but “overly optimistic,” and then, not having much of a hammer to hang over their heads if they skipped treatment, resulted in significant failure. Parish Prison, in those days, had really good food. Time Magazine had an article on various city jails and parish prisons in the United States, and New Orleans Parish Prison was voted as being among the top places to stay for food, at that time. So, that study was a total flop, and it told me that I’d better put my efforts elsewhere, that these patients were too far gone to really step in and do treatment with them, after they had been in jail for 50 times or more.

TB: You mentioned the name of Jerry Levine, the successor of Jonathan Cole.

DG: Actually, we might have written something together for the Psychopharmacology Research Branch, I think, but it slips my memory right now. Jerry was a good, good influence following Jon

Cole. That was a very good selection and he continued along doing some of the good things that Jon did, so he was a definite help to us also.

TB: You also did some work with Leo Hollister.

DG: Yes, and with George Simpson we did some collaborative studies, and also with Arthur Sugerman. I think we also did one study with Sam Gershon, but I'm not sure.

TB: What did you do with Art Sugerman?

DG: I'm trying to think. I think it was one of the drug studies, because I know we became very friendly over one of these studies that we had. It just slips my memory.

TB: Is there any other drug you worked with that you would like to mention?

DG: Well, thiothixene was a relatively good drug at that time, because the sedation was much less than it was with some of the other antipsychotic drugs, and it's EKG effects were practically nil. So, we felt that was a nice drug to work with. We were also looking at the EKG's of our patients and it was very clean in that area compared to Mellaril.

TB: You got interested in side effects very early and published extensively on side effects.

DG: Yes, I published also on the hematologic side effects of Serentil.

TB: Then, you became involved with alcoholism and substance abuse. Didn't you direct a substance abuse center?

DG: Yes, I was Program Director for the southern part of the state at that time, from 1962 until I retired from the state in 1990. And, during that period of time, I was the only psychiatrist from Mandeville, on the other side of the lake of New Orleans. I was responsible, this sounds rather absurd, but I was responsible during those 30 years, or so, for almost 10,000 patients, who came through our inpatient and outpatient program. And, one thing I'm proud of, probably the thing I should be most proud of, every one of those patients had my home phone number and my work number. I had a card that I would give out to every patient that came through our clinic or our inpatient program and to every patient that came through my VA program, which I ran later on, while I was running the state program. I started that in 1985. Every patient always had my home phone number and my work number and they knew they could call me anytime they wanted to.

TB: So, you were always available to your patients.

DG: My schizophrenic patients, the schizophrenic families, or the patients, themselves. This was very, very rewarding. It was very rare when a patient took advantage of it. Rather than tell a

patient I was going to see him in a week, I would have him call me in two days and let me know what was happening. We might even increase his dosage in 3 or 4 days, not having to wait a week. And, I was able to escalate the dosages more rapidly. It was very rewarding for me and to the patients. And, the patients sometimes would almost go into shock when you gave them a card with your home phone number and your work number, so it made for a very good automatic doctor-patient relationship to start off with. In fact, when I was doing the Fischer Project and running the free medical clinic, I was doing house calls in the project. I wouldn't do that nowadays. This is back in 1969 through '75, or so. Then, there were a lot of knives and only a few guns. Now, there are a lot of guns and a few knives. I would make house calls with the president of the TCA organization, an African-American. We'd make house calls together. One time, the president came to see me, and said, "My aunt just came down from Connecticut and she was in a mental hospital up there. Now, she's flipped out again. Can you come and see her? She's got a butcher knife in her hand." So, I said, yeah, but you're coming with me, of course. So, we went into the apartment to see her, and there she is, holding up a huge butcher knife in her hand saying, "I'm going to be killing someone or kill myself because the voices are telling me to kill someone or kill myself." She looked at me, I had my white coat on, and said, "Who are you?" and I said, "I'm a doctor." She said, "You're no doctor; doctors don't make house calls." I cracked up and started laughing. This fellow, Keith, the president, started laughing and she started laughing and put the knife down. So, that was a wonderful episode, a wonderful scene.

I'll probably remember that on my deathbed. So, all of these things were very, very rewarding and I think that was the most fun part of what I was doing, so I think it was well worth it.

TB: It seems that you had numerous activities simultaneously.

DG: Yes, we were too far spread out. But when I look back, I sometimes think I should have devoted almost all of my time to psychopharmacology, and yet, when I look back upon my memories, I'm very happy I did all of that crazy stuff.

TB: Didn't you also study sexual behavior?

DG: That was a joke. I really didn't study that. What happened was that there was a magazine called *Medical Aspects of Human Sexuality*. I don't know why they called me to write two articles; I thought it was a joke, but they were offering to pay me \$250.00 to write an article on

something I didn't know about so I said, great. So, one article was on Sexual Positions during Pregnancy. I thought I would play a joke. So I went ahead and wrote that the best position is the pes caelum position, which meant "foot on the sky." The editor corrected it and changed it to "foot on the ceiling" position and published it. They gave me \$250.00 for that. I thought, hey, this is a great occupation. That was a good deal of money for an academic back in the 1970's. I mean, you can publish anything you want in this magazine and get revenue. And, then, there was some other article, I've forgot what the title of the article was, but in the references, I had one reference as something about "how to grow aphrodisiacs in your garden" by William Shakespeare. They published that in the *Medical Aspects of Sexuality*. I also worked with pipotiazine palmitate. Do you remember that?

TB: Yes, of course.

DG: A drug with a very long half-life. One injection lasted almost four weeks. I don't know why it never became commercialized in this country, but it worked very well in the chronic schizophrenic population. It was the first significantly long-acting neuroleptic. It was an ideal drug, once every four weeks, or three to four weeks. Anyway, in my introduction to the study that we did, I wrote that this compound had such a long duration of action that it must be slowly metabolized by the liver and probably would work well in people who had the "Simpson syndrome." And, in the next sentence I added in reference to the "Simpson syndrome" that the drug is only slowly metabolized in the liver when drinking "First Growth" wines. When I mentioned the "Simpson syndrome" in my presentation at the ECDEU meeting, everybody got a good chuckle out of it. Then I used that presentation to cite that as a reference in the article. It was a joke, but, it was fun at that time. I was somewhat of a mischievous character at times.

TB: When did you get involved with medical ethics?

DG: I must have had some guilt about my mischievous behavior. It was when Phil May was president of the ACNP back in 1973 or '74, around that time. Phil was a fantastic person. He was the British version of Heinz Lehmann, very gracious, and if I remember correctly, he was the first investigator to perform a comparison study of psychotherapy with drugs in schizophrenia. Chlorpromazine was the drug used because it was an early study and the study was chlorpromazine plus psychotherapy, vs. chlorpromazine alone vs. psychotherapy alone. I believe that was it.

TB: What did he find?

DG: Psychotherapy by itself was like placebo in those schizophrenic patients. In these studies, chlorpromazine by itself is significantly better than psychotherapy in schizophrenics and psychotherapy added nothing to the efficacy of chlorpromazine. That was really the conclusive study showing that all this nonsense by Brody and Redlich, the schizophrenogenic mother, and John Rosen, direct analysis, was useless. I was Chairman of the Ethics Committee of the ACNP, at that time, and he asked me to start drawing up the guidelines, stating the principles of Ethical Conduct for the ACNP, and that was time consuming. As a matter of fact, it really took a lot of my time. I really got involved in that. In fact, at the time, I asked Dave Mielke to take over as principal investigator of our ECDEU grant, because I was spread too thin. I was overly involved in developing the Statement of Principles at that time. I think it was the first Statement of Principles or Ethical Code developed for any medical organization. Psychology had their own, but not any medical organization or research organization that I'm aware of, as far as medicine was concerned. So, I spent about two years on that, not just myself, but with Bob Force, a lawyer at the Tulane Law School, and the entire membership of the ACNP. I sent out several drafts to get input from every member of the ACNP, and then, reviewed all of these inputs. Most of the members returned it with their comments. Reviewing these comments and trying to incorporate them was a much greater job than I realized it would be. Since Phil May had asked me, I felt obligated because I felt indebted to him as a person. He was just a fantastic individual. And finally, we finished it after about two years and it came to a vote by the membership. I think we had about 162 members, at that time, and only one member voted against it. I thought to myself, out of all these eccentric people who belonged to the ACNP, to have only one person to vote against it, that's a fantastic accomplishment; so I was well satisfied at that point. Of course, we modified it again in 1984-85, and it has been modified and changed quite a bit since that time, as the years passed. But, that was a very intense piece of work, and it made me examine a lot about what I was doing. It was very educational for me, because I learned a lot. Bob Force and I later edited a book on Legal and Ethical Issues in Human Research and Treatment that had the Imprimatur of the ACNP. We had Albert Jonsen, Angela Holden from Yale, Alan Stone, Karen Lebacqz, Robert Levine and other contributors. Also, Father McCormick up at Georgetown was another person who was very sharp in this area. So, it exposed me to quite a few people outside

the field and was something I can thank the ACNP for, because I never would have got involved in that area, were it not for the ACNP.

TB: You also wrote several chapters in that book.

DG: Well, actually, it was a book on *Ethical Informed Consent for Research and Treatment*. I felt that was a complicated area for schizophrenics, and still is.

TB: It was a very successful publication.

DG: Yes, we had a good number of reprint requests. In fact, there was a spin off. I was invited to a number of areas to give lectures. It was unusual at that time to have the Principles of Research, which really had some legal implications. I think the one person that voted against it was afraid of legal implications. I received invitations to participate in some symposia in Michigan and in Boston. It exposed me to different areas and I think I became quite knowledgeable in this area.

TB: You also wrote a book on alcoholism, didn't you?

DG: I wrote a book on alcoholism by myself. That was probably one of the things that I did that required more time than anything else. It was *Early Diagnosis, Intervention and Treatment*; describing, not only diagnosis, but the various types of intervention techniques, and then, various types of treatment modalities. Treating alcoholism is a difficult problem; the noncompliance rate is quite high but no different from asthma or high blood pressure. The idea that you have a genetic susceptibility for alcoholism, as well as for high blood pressure, asthma, and diabetes, and comparing that in these terms makes it more acceptable as a chronic medical illness. I've also written on this area as far as the relapse rate or non-compliance rate, showing that non-compliance rate in alcohol and drug addiction is not that much more significant than non-compliance rates in diabetes. In fact, in one survey study of diabetics, where medication was prescribed by their physician, approximately 50 percent did not take their medication as prescribed. Pretty shocking that it was almost as high as the non-compliance rate with alcohol and drug addicts. So, one relapse, to me, should not be regarded as an end-point event any different than relapse with diabetes or high blood pressure. About 50 percent of hypertensives don't take their medications, as prescribed, at one time or another. The worst case of noncompliance that I use in teaching medical students was published in *Lancet* about 12 or 14 years ago on congenital hypothyroidism. Almost half the mothers were not giving thyroid as prescribed for the children. That, of course, is incredible. By trying to get people to understand non-compliance not being that different in alcoholics and drug

addicts than other medical illnesses, I felt like I could make it more acceptable to the public to have less negative reactions and I always felt that this was very important. I think that psychiatry has always had a problem in the area of acceptance in one way or another, lesser nowadays than years ago. When I first told my friends I was going into psychiatry, my best friend stopped talking to me for two days.

That's a true story. He said he was going into Internal Medicine and went up to Mt. Sinai and became an outstanding internist. He said to me, "You're leaving medicine; you're deserting us." So, psychiatry has had a tough row to hoe, as far as being accepted.

TB: North American psychiatry was almost entirely psychodynamic at the time you entered the field, but it seems that New Orleans with Heath was biologically oriented.

DG: Right.

TB: So, in a way, you were lucky.

DG: I was very lucky. He gave me a chance to get my feet on the ground and I can thank him for that.

TB: Were you involved in psychodynamic psychiatry at all?

DG: I wrote a little paper one time for GPs on how to treat primary general practice patients psychodynamically, but actually I'm a bigger fan of the systems that they worked out in recent decades, the interpersonal therapy, the cognitive behavior therapy model, and also, more recently, the cognitive behavior systematic analysis model for depression. I'm much more impressed by their results as they're easier to evaluate, easier to research, in a sense. I've read the Interpersonal Psychotherapy book by Weissman and Klerman, because I have to teach part of that to my residents and discuss it with them when they're seeing patients. When I retired in 1994, Tulane was very nice to me. Since I put in 40 years of teaching, they made me Professor Emeritus and let me have this office across the hall and a secretary to work with. I don't get paid. This way, I'm in control of my life, which was never true before. I come in three days a week, on Mondays, Tuesdays, and Wednesdays, teaching medical students, the freshman, sophomores, and juniors; and I also teach the psychiatry residents, the first year and second year psychiatry residents. The areas I cover with them are the psychopharmacology of anxiety and affective disorders, and schizophrenia. I also teach group therapy techniques, and alcohol and drug abuse. Those are the

main subjects. It keeps me feeling young and it keeps me with young people, which I think is very, very important, so my marbles don't get too rusty.

TB: So, you do that three days a week?

DG: Yes.

TB: And, the rest?

DG: The rest of time I'm reading. I was accumulating books that had nothing to do with medicine for many years, looking forward to the day when I retired to read these books.

Nowadays, actually, I read more medical journals than I did before, because I didn't have time before, but I also read more novels, both fiction and non-fiction, now, than I had. Of course, I have much more time to do that, because reading, to me, is a major part of my life. The only problem I have is in my compulsiveness, to some extent, when new books or magazines come out, I don't have the ability to turn them down, whether they're medical books or non-fiction or fiction books that have nothing to do with medicine, so I keep on buying books and magazines: for example, *The New Yorker*, *Scientific American*, *The N.Y. Review of Books*, etc. I've never caught up with all these books that I've been saving to read in my retirement. So, it's a tremendous cycle I'm going around in, but I hope I never catch up. It's fun.

TB: So, you read a lot.

DG: I read an awful lot. I read more than ever before. I'm always calling up George Simpson to tell him about something I've read. He does that with me. He reads a lot, also.

TB: Do you keep close contact with George?

DG: Yes, I've always felt that George and I had a lot in common, despite our tremendously different backgrounds, and we've always had fun with each other, and I like to think that attracted us as well as our interest in food.

TB: Good food.

DG: Yes, we both enjoy good food. That's one of the reasons I stayed in New Orleans. When I look around the country and think of different opportunities, Kansas City, oh my God, I couldn't handle that food, and my wife enjoys good food, so we had no choice, really, we had to stay. And, it's a very interesting town. We live out in a suburb, in an area that's only about twelve minutes from downtown, and yet, it's totally different from what you see downtown, the French Quarter and the French Market.

TB: I remember when we had an ECDEU meeting here. I also remember the hospital you worked in those years. We were traveling for two and a half hours to get there.

DG: Yes, but we have an interstate now. At the time we had the ECDEU meeting down here, one time back in the 1960's, I forgot what year it was, we had a meal at Antoine's. Were you there?

TB: Yes. That was in 1967 or '68.

DG: Yes. And what happened was that I think I asked for each ECDEU member to chip in about \$10.00 or \$12.00. The wine we were served that day was a Chateau Pontet Canet. I remember this, because I had to pay for part of that wine out of my own pocket. Arnold Friedhoff got up at the end of the meal and toasted me, saying something about, how fantastic.

They got their money's worth and I was thinking to myself, yeah, your money's worth. Part of that was my money.

TB: Arnold just died.

DG: Yes. We'll all miss him.

TB: The ECDEU meeting we had here is quite memorable. We have many photographs from that meeting in CINP's international photo archives.

DG: Oh.

TB: Let me switch. Could you tell us something more about your involvement in group therapy?

DG: I enjoyed group therapy very much. I'm doing group therapy right now. Actually, we had a group therapy association, Louisiana Group Therapy Association, as part of the National American Group Psychotherapy Association, and I was very involved in it. We had no one to teach us that in 1962 and '63, so I used to meet with four or five prominent psychiatrists in town, one night a week, from about 8:00 to 10:00, I guess. We'd supervise each other, criticizing each other, and reporting on our groups. That was the only way we could learn because we had nobody to teach us. There was somebody named Hugh Mullan up in New York who worked with group therapy. He was very good. We had him down as a guest. I was enjoying it so much; working with alcohol and drug addicts, the group phenomenon naturally takes place.

That's what some of us call the pseudo-cohesiveness, false feelings of togetherness when we first meet somebody who has the same background we do. Example: when I was overseas in the Air Force, in the Philippines, I hadn't met anybody from Brooklyn, New York in a couple of months, which is unusual, because we had a couple of million people living there. Then, one day,

somebody came over to our Air Force base and I met him, another doctor. He was from Brooklyn and he went to the same high school I went to, Boys High School. Before you know it, you start getting close to a person, even though you know nothing about him. That's what I call pseudo-cohesiveness, false feelings of togetherness. Of course, later on, about two or three months later, I found out he was a real terrible person, and I didn't like him at all. So, sometimes our first impressions are not the right ones. But, in the beginning, alcoholics have this automatically happening to them. "Oh, you're an alcoholic; you go to AA. What AA group do you go to"? So, they fall, naturally, into this group phenomenon, and they're easy to treat with group therapy, much easier than other types of patients, I think. Nowadays, most of them are mixed drug addicts and alcoholics, but they still have this AA approach or NA (Narcotics Anonymous) approach. I started to really enjoy group therapy because it flowed so smoothly and so evenly and we worked out some techniques that I think worked quite well. And, at the same time, I started realizing, early in treatment programs, that if you didn't deal with the spouse, you're missing out on a gigantic part of the patient's life, and each one of us sees the world through our own eyes. The more eyes you have to help you see the world, the more valid the observations become. So, I started putting this practice into married-couples group therapy, treating six or seven couples at one time. I used to do this on Wednesday afternoons, two groups, one from 1:15 to 3:15 or 3:30 and the other one from 3:30 to about 5:30 or 5:45. And, they were coming from Baton Rouge, because I was the only one doing this for the state. They also came from Lafayette, Louisiana, Cajun country, and they were people who were fun to deal with, especially the Cajun population. They love to drink and they love to talk, so they are very good patients. And, I found out that when we did a follow-up on the first 160 couples that we treated, this was back in 1969 or '70, only two of them had separated in the eighteen month follow-up, which was probably below the national average. And, my success rate, as far as abstinence and decreased days of drinking was much higher because that was a select population I was dealing with. Of course, if they're still married, that means they have a support system, and if they're still married, they're more likely to have a job, so you have more positive predictors working for you by just treating married couples. You have a much better chance of success in treating this kind. So, I think, that also added to my enjoyment, because I might have been finding failure in one area, but I was finding success in this area, which automatically had a higher success rate, just by the availability of good support systems. So, that

made it much more fun. You need to have some successes for positive reinforcement with a group that's difficult to treat.

TB: What about drug therapy?

DG: I should say that one of our former residents, Chuck O'Brien, showed naltrexone efficacy very nicely, along with Stephanie O'Malley from Yale. In two separate double-blind studies, they showed how naltrexone does decrease the number of drinking days, and also, decreases craving to some extent. The data are solid. I think, two separate studies done without each one aware of each other, coming up with the same results, even though it's in only two studies, was impressive proof of the drug's efficacy. So, we now use naltrexone frequently. Oh, one other thing I forgot to tell you. I used to consult on the college campus two half days a week, treating Tulane uptown college students. I started going on Tuesday afternoon and Friday afternoon, it must have been about 1973. In 1975, I stopped the free clinic in the Fisher project area. I started going Tuesday afternoons and Friday afternoons to the Uptown Campus at Tulane to consult and treat undergraduate students, which was a nice change of pace from drug abusers and schizophrenics. It was like ice cream, soda, and candy, to consult and treat college students. They had a number of eating disorders. In bulimia cases, I used naltrexone, not in a research study design, but case by case, and had some good results with a few cases, in decreasing the binge eating and euphoric responses to carbohydrate binging. At the same time, I had the opportunity to participate with a naltrexone nationwide VA study with Leo Hollister, who was on the committee to look at the data for using naltrexone with heroin. Of course, those were very disappointing data. The patients would stop taking it. With the naltrexone in bulimics, I had patients, who were afraid to leave town when they graduated, afraid they might not get the naltrexone, elsewhere. So, it did help a sub-group of bulimics. But, I wasn't running a controlled study in that group.

TB: So you were using naltrexone in bulimia? What about Antabuse (disulfiram) in alcoholics?

DG: I always used Antabuse, but I always tried to get a support system to supply it to the patient. If there was a wife, I'd have the wife give the Antabuse to the patient. I would tell a patient, you're not taking it just for yourself; you're taking it for the family structure. And, if they didn't have a family and they were working, and had an employer, I'd have the employer give them the Antabuse. So, I tried to bring in support systems to administer the Antabuse. Of course, the original Antabuse study with controls was done by Fuller, up in Cleveland Clinic, before he joined

the NIAAA. He did that in 1973 or '74 and found no higher abstinence rate at the end of nine months, but he did find a significantly higher number of days of abstinence in the Antabuse group. But the abstinence rate was only twenty percent or less in nine months. So, just seeing that data, you automatically realize if you have a support system, use them to give the Antabuse, with the patient's permission, of course, this might be beneficial.

TB: What else were you involved with?

DG: Just teaching and supervising. You have to be careful with Antabuse therapy in schizophrenics, because Antabuse does inhibit dopamine β -hydroxylase, and you don't want to increase their dopamine too much. So, in schizophrenics, I would just use a placebo dose of Antabuse, 125 mg/d. We did have a problem with our schizophrenics, who were crack abusers using the atypical antipsychotics, like olanzapine, 20 milligrams or Risperdal, 6 or 8 milligrams/day; our "crack" using schizophrenics had a little bit more of a response problem. I think George Simpson made some similar observations. Our patients would become more outgoing, their thought dissociations might decrease, but sometimes the paranoid delusions and hallucinations persist. I found myself getting desperate and would add a small dose of a dopamine-D₂ blocker on top of the atypical antipsychotic, and then, in some cases, the voices would go away. Now, I haven't done a double-blind study, but I have a suspicion that the reason is that cocaine causes renal vasoconstriction with a decrease in blood flow and also vasoconstriction in the brain vessels resulting a subsequent decrease of perfusion in the brain. Perhaps, not all of our drugs are getting through to the right areas and these patients may need more of a kick with a dopamine-D₂ blocker, in addition to atypicals. But, that's been an observation of mine, and I think, perhaps, George agrees with me. The dual diagnosis patients we wrote about back in 1979, have increased, dramatically, as the years go by. I guess there are several good chemical reasons for that. I had an interesting experience about this problem, by the way. The original report on the incidence of alcohol and drug abuse in primary psychiatric patients came out of the Bronx VA Hospital in about 1975 or maybe a little bit earlier. The incidence of alcohol and drug abuse in these primary psychiatric patients was almost sixty percent in an urban psychiatric hospital. At Charity, we were running about the same percentage. Anyway, at Wisconsin, they asked me to come up there for a three day seminar on alcohol and drug abuse, about twelve or fourteen years ago. I was giving them the data about the incidence of dual diagnosis problems in our primary psychiatric patients

and I made the statement, "I guess, here in Madison, Wisconsin, you're not going to have this high incidence, because you don't have that much of an intense urban situation going on." Well, I guess they were too polite to disagree with me, but, anyway, about two weeks or a month later, I received a manuscript in the mail from a PhD psychiatric social worker with their data showing me that the incidence of dual diagnosis in their study was about forty to fifty percent in the primary psychiatric patients. So, it didn't seem to matter wherever you live, you're going to have an increasingly high incidence. It's a real problem nowadays, because it contaminates drug studies, and particularly, in outpatient studies, it's a disaster. It was much easier to do studies years ago.

In fact, there was a study done in New York State, I reported on, for the journal of *Alcoholism: Clinical and Experimental Research* about thirty years ago on the incidence of depression, anxiety, and schizophrenia among primary alcoholics. It was done in sixteen or seventeen different units in New York State. The incidence was only about ten percent, or so.

Nowadays, we see a much higher incidence of substance abuse problems in our primary psychiatric patients and vice versa. It's gotten much worse.

TB: Besides naltrexone and Antabuse, did you use or study any other drug in alcoholics?

DG: We tried lithium, which turned out to be of no value in alcoholics. We did a lot of antidepressant studies in primary substance abusers, but we didn't do long-term follow-up to see if it had an effect on abstinence.

TB: You mentioned using SSRI's in alcoholics.

DG: Of course, the Toronto Addiction Research Center, which is one of the best on this continent, reported a short term study using sertraline, I think, in a one month study to decrease alcohol intake. This was some years ago, and because of their findings we tried it, but we didn't do it in an adequate double-blind controlled study. So I can't be objective about it. When you're doing double-blind studies in this population, you have to sort out those with major depression and eliminate them, you know, just to see if a pure SSRI can reduce the alcohol intake.

TB: Do you have a preference for any antidepressant in alcoholics?

DG: Well, I like short-acting compounds, so I would choose sertraline, something that's a little bit more pure as far as affecting the liver.

TB: What about doxepin?

DG: I would not use doxepin now with the SSRI's available. I would say that cardiac wise, you're better off with SSRI drugs. In fact, our alcoholic population seems to be more sensitive, now this is subjective, to anticholinergic side effects than our non-alcoholic population. I have no idea why; it just seems that way to me. I have more complaints in that area. So, I tend toward the SSRI's for depression in these patients.

TB: Do you remember which antipsychotic drug you studied first?

DG: We might have done work with Stelazine, trifluoperazine. And, then, we used that as a comparison to a newer line of drugs in comparison studies.

TB: Which was the last antipsychotic you studied?

DG: That's a good question.

TB: Did you work with any of the atypical antipsychotics?

DG: No, I handed over the unit to Dave Melke before the atypical came out.

TB: When did you hand things over to Melke?

DG: In 1977, somewhere around that time, when I became overly involved in the ethics code and substance abuse.

TB: Didn't you work with penfluridol about that time?

DG: Penfluridol was one of the last compounds I probably worked with. It was a beautiful medication in our patient population. You gave it orally once a week and it worked, as far as antipsychotic activity was concerned.

TB: There was a paper published recently on the effect of penfluridol on the EKG.

DG: Is it used in Europe?

TB: At a certain point in time, it was used very extensively, because it is a selective dopamine-D₂ blocker.

DG: The side effects were minimal. I had fantasies of using that compound where I would train a high school graduate, to make house calls once a week on my schizophrenics, who were living at home or in a residential home, giving them the medication orally. Another compound, I worked with was sulpiride. Now, that was a clean compound. We did studies with that. We didn't find any side-effects, to speak of, in our chronic schizophrenic population, and it's quite an active antipsychotic compound. In Europe there were some controlled studies showing that it was also an antidepressant compound.

TB: When did you study sulpiride?

DG: That was about in 1976. That might have been the last compound that I did and I thought that was clean. I have no idea why that didn't go any further here.

TB: The benzamides are very successful in Europe, but they are not used in North America.

DG: I don't know why. They are cleaner than the atypicals.

TB: Did you work with clozapine?

DG: No, we didn't have that opportunity. Herb Meltzer was doing it. Herb started about 1980, I think. But, sulpiride was, I thought, another ideal drug. And sulpiride and penfluridol were two of the nicest drugs that came down the line and they didn't become commercial in this country. Well, you mentioned the possibility of EKG problems with penfluridol, which I'm not aware of, but that would be something to think about. TB: Are you still using haloperidol extensively?

DG: No. I may use it every now and then; sometimes intravenous haloperidol. For example, in a mentally retarded patient who had chewed off her fingers, while putting on a cast to protect her from further damage, we used intravenous haloperidol. But, otherwise, I tend to use more of the atypicals. One reason for not using antipsychotics too quickly is that someone might come in with a PCP psychosis, which might look like schizophrenia, and the patient clears up after given an antipsychotic, and you will not find out what the basic problem was.

TB: Well, you also studied withdrawal effects of neuroleptics, didn't you? You had a paper on that some time ago.

DG: Oh, actually, I think that was one of the mistakes that we made.

TB: Yes.

DG: What happened in one of our drug studies, I forgot what compound it was, it was a phenothiazine derivative, for some reason or other, we just stopped the compound and we had rebound nausea coming up as a result. I regarded that finding as a rebound phenomenon, but that was a mistake I made. George Simpson corrected me on that, because we also had suddenly stopped our antiparkinson drug and it was really a rebound from the anticholinergic, a cholinergic response with nausea. It was a response to the withdrawal of the anticholinergic antiparkinson drug and not to withdrawal from the antipsychotic drug. So, I was a little embarrassed about that.

TB: What about antidepressants? Which was the first antidepressant you studied? Wasn't it desipramine?

DG: Yes, that was the first. We might have studied one or two other antidepressants that had a number but were no better than placebo. In the beginning, when we arranged to do double-blind studies at the Charity Hospital outpatient setting, we were trying primarily to concentrate on depression. We might have used one or two compounds in the beginning. Desipramine is the first active compound we tested that showed up in our depressive population as having definite activity as compared with placebo. And, it still is a very nice compound.

TB: Which was the last antidepressant you studied?

DG: I'm not sure.

TB: You had also been very much involved with the benzodiazepines. Weren't you on a committee on the benzodiazepines?

DG: Yes it was the APA committee.

TB: Would you like to comment on that?

DG: Carl Salzman was also on that committee, I think, and some others, of course. It was a committee to evaluate the addiction and dependency problems of the benzodiazepines. The recommendation was that there were some people that were possibly more susceptible to addiction, but the overall opinion was these drugs could be handled quite comfortably if the patient had the correct diagnosis of Generalized Anxiety Disorder. Otherwise, there was an addiction potential. But, actually, the data on the benzodiazepines was sort of interesting, in a sense; I had a run in with the manufacturers of alprazolam. When I was a member of the FDA advisory psychopharmacology committee, alprazolam (Xanax) had already been approved to treat Generalized Anxiety Disorder. I was given the assignment by the FDA committee to evaluate its antidepressant activity because the company wanted to market this drug as an antidepressant as well as an anti-anxiety agent. Now, there was a suggestion to compare it with placebo. But, I had a great deal of concern, which I expressed in my report to the FDA psychopharmacology committee, that if that was put into the PDR as a primary antidepressant, patients with depression were going to get addicted to this compound. Of course, they could be more susceptible in that sense with their anxiety that accompanies the depression. The data showed that it didn't seem to be as effective as our primary antidepressant medications. But I was concerned about alprazolam being included as a primary antidepressant and officially approved. So, the company did give me somewhat of a hard time. Depressed patients with low self-esteem could be more liable to the potential addictive properties of benzodiazepines if there was an inadequate antidepressant

response. It never did get approved as a primary antidepressant, and I was sort of happy to see that happen. I didn't think it was needed in that area. And, the other thing is, in our alcoholics, while we don't have any objective evidence that the incidence of the benzodiazepine dependence is any higher than it is in the general population, at the same time, we do have some data that suggests that alcoholics may be more susceptible to benzodiazepines addiction. Ciraulo, in Boston, has published some data on adult male children of adult male alcoholics on a euphoria rating scale, comparing 1 milligram of alprazolam vs. placebo, in the adult male children of male alcoholics. They seemed to score significantly higher on the euphoria rating scale on these drugs than they did on placebo. So, those suggestions make me a bit worried. I've seen these benzodiazepines spread out too much across the world.

TB: During the years you were involved in clinical trials with psychotropic drugs, major changes were taking place in the methodology of clinical investigations.

DG: Of course, when I was at NY Gowanda State Hospital in 1954, not only did they use insulin shock, but they were using ice cold baths. You know, when I saw that I just went into shock myself. They had these patients tied, the ones who were agitated or sullen, had them tied in restraints surrounded by ice bags. I mean, it was like a horror movie. So, yes, I saw things that I shouldn't have seen. I was too young. I never did see a well-controlled study of insulin shock therapy.

TB: Do you remember when the BLIPS system was introduced?

DG: Oh, I think it was a tremendous addition to the psychopharmacology evaluations getting onto objectivity. I used to brag that psychiatrists, years ago in the sixties, psychiatrists were more objective as the BPRS came along and then the BLIPS system came along, in their drug evaluations than internists and other medical specialists, even though they were giving us psychiatrists a hard time about being so subjective. We were actually, more objective in what we were doing. And I felt good about that.

TB: At the time you started, there were no ethics committees, no patient consent forms.

DG: Well, we had to get the patient consent at the Jackson, East Louisiana State Hospital to move them on to the research unit. So, on the consent form, it said that these patients would be receiving investigational drugs, that the families would be notified, if they had any objections the family should tell us, and that we would give them the results. But, of course, these families were, for the

most part, emotionally if not physically, separated from the patients. So, a part of that, you might say, was hypocritical because we knew that the families would not respond to us. Ninety percent of them did not respond to us. Ten percent did, I would say. We also had to obtain judicial consent from the local judge. So, the consent was, sort of, paperwork consent. That's one of the things I questioned, myself, later on, when I was doing the statement of principles. I had questions of my own approach to research. And, I think that was a very healthy thing to do. Now, with our alcoholics and drug addicts, we always obtained consent from the patient, so it was something that we did without thinking. It was part of our routine. It wasn't as good as the informed consent is now. It wasn't as detailed, but the patients were told that at one time or another they might not be receiving an active medication. We told them the potential risks and benefits as well. I don't ever remember doing a study without a written consent.

TB: So, you did have signed written consents from the beginning.

DG: I think what happened was that because of Heath's research, the type of research he was doing which had some real dangers, putting electrodes into the brain, he already had to work out a consent sheet because of the medical school's insistence. So, that might have had some type of spin-off effect with us in psychopharmacology that automatically consent sheets were to be done. Dr. Heath's research was going on before we even had these psychopharmacology grants. So, consent was expected of us, I guess, when we started off, not by the department but by the medical school.

TB: Were you the one who implemented the program in alcoholism in Tulane. You ran it for well over twenty-five or thirty years?

DG: I didn't actually implement it, but it was somebody who was a vice president of a prominent clothing store. He had a brother, who was an alcoholic.

TB: When was that?

DG: This was 1961, and he had a lot of influence in the state legislature, and so, there was a building built for student nurses at the psychiatric hospital in Mandeville, very large beautiful grounds; this building was to house the student nurses, while they rotated through their training. The contract fell through at the nursing school. So, they had this beautiful empty building. It was the perfect building for treating alcoholics and drug addicts. There were thirty-two beds, males on one side, females on the other side, no more than two patients to a room, private bathrooms. It

was one-story, when they walked out of their rooms, there were the piney woods, just unbelievable. It all happened by accident, of course. Nothing like this is ever planned. Often you plan something, it turns out horrible. This happened by accident. He was able to get that building and get the funding to run the program, and he's the one who started it. His name was Simon Marx. I remember him well, a big, hefty man. He's no longer living. He was very outgoing and knew what he wanted. So, I had this building and this state funding; it was a part-time civil service job, which helped me a lot. I was only making twelve thousand dollars a year, with my psychopharmacology grant, and I needed some extra money for my family. So, this was a civil service job, a part-time job that I had, that helped me get along financially, because I never did enter private practice.

TB: So, you were never in private practice?

DG: No.

TB: But, then, you ran this program until when?

DG: Until 1998, when I retired from this area.

TB: Can you tell us something about the program?

DG: The Alcohol and Drug Treatment Center?

TB: Yes.

DG: I had a lot of emotional investment in that, because of the staff and the patients, I did a number of things with that program that nobody else does, I guess. Because of my time limitations, I was over there just two days a week. On Monday, I'd be there from twelve noon until, say, five o'clock in the evening; and then, I'd be there on Thursday morning about five thirty a.m. We would wake up the poor patients early. It was a terrible thing for me to do to them. I then left at 1 p.m. for Tulane. I had to come back to Tulane, to be on campus at Tulane. And so, within that limited period of time, I did a lot of things. I had to run ward meetings twice a week. But what I did was, I'd have the nurse call me every day at home, in the evening hours, and make ward rounds on the phone, one patient at a time. If the patient had to talk to me, I'd talk to him on the phone, so I could get some of the work done on the phone. I used the phone an awful lot. Either the patients would call me, or the hospital would call me to do ward rounds. Then, when I went there, I would do group staffing. Instead of doing staffing with a patient, one at a time, I'd staff three patients at a time and have them interact with each other. I called it a group staffing procedure, which I published. That meeting would last for about two and a half hours, three patients at one time for

three hours, rather than on one patient for an hour and a half each. I got them to really interact with each other and it became an accepted routine. Patients are interesting, very fascinating. You'd think they'd be too embarrassed to talk about their problems. We would talk beforehand about any sexual problems, or their personal problems that they wanted to talk about in private. The medical students, four or five at a time, would sit in with me, as it was an excellent learning experience. We did a group family session, later on that day, with three or four families at one time, going over the history, getting the information, and so forth. So, it was a very intense type of treatment going on, and these patients made good progress. It was all through the group process. The follow-up would be in married couples' group therapy or regular group therapy. Then we had the ward meetings, which I do Mondays and Thursdays, plus the phone rounds. I had some excellent counselors that I trained, who did a lot of behavioral work, as far as implosion therapy, desensitization, and social phobia problems like fear of heights we see with these patients. When you do surveys on them, you find out the incidence of phobias are sky high in this population, but you don't find out unless you ask them specifically. We had an eighty-two items Fear survey questionnaire. We were trying to make sure that we didn't leave any phobic thoughts out. We also standardized a relapse prevention inventory, an RPI, that I read in Lancet to prevent relapse. And, we did a lot modeling, a lot of role-playing, in addition to the group therapy and individual counseling. I'd have my social worker take the patient up to the top of the Trademart tower, step by step for desensitization, or all at once for implosion therapy, keep them looking out over the side of the building until their panic subsided, and then, feed them a candy bar or ice cream for positive reinforcement. It really worked and you just had to keep them trusting, stay with them looking down from the top of the building. And so, we did a lot of behavioral work, in addition to the individual and group work. I used Antabuse in my alcoholics about ninety percent of the time. If they were married, the spouse gave it to them. If they were crack addicts, I automatically talked to them about Antabuse, because there was a study done in Arizona that even if those crack addicts who were not alcoholics, drink socially; they were about seven times more likely to relapse compared to other crack addicts who didn't drink at all. So, because of that, I tried to give it to crack addicts, and then, I would say, "Antabuse might be an additional safeguard here." It's now even more interesting since Chuck O'Brien published on the ability of Antabuse to elevate blood cocaine levels and cause uncomfortable symptoms in crack addicts. Some crack addicts were

really highly motivated to take Antabuse, even though they weren't alcoholics. Very interesting! We had our dual diagnosis patients at the VA, when I was running that unit from 1985 to 1998. In that program, we had a separate dual diagnosis group going on. In group therapy with dual diagnosis patients, we were a little bit more didactic, a little bit more educational, and less confrontational. You don't hit the denial mechanism as hard. You've got to provide some social outlets for them to want to give up their alcohol and drug abuse. You have to go slowly with them and tolerate more relapses from them, particularly in the beginning of therapy.

TB: During the years you worked with many people. Could you tell us something more about Mel Bishop?

DG: Yes, Mel Bishop, of all the people I worked with, was the most helpful and the most valuable, because he taught me a lot. He was a very retiring person, who didn't come on assertively. He was very intelligent.

TB: What happened to him? Didn't he move to work in the pharmaceutical industry?

DG: Well, Lederle pharmaceutical gave him a very good offer financially. The salary of a psychologist just wasn't high enough and Mel had four children. Some of them were already grown. They were going to college and he needed the money, I guess. But, anyway, he went to work for Lederle. Harriet Kiltie is the one who hired him away from us. So, Bill Swanson took his place, later on. Swanson was a sociologist-psychologist who could handle statistics.

TB: I have not heard about Mel for a long time.

DG: Shortly after he retired from Lederle, he developed bladder cancer. In fact, I wrote Mel's obituary for the Neuropsychopharmacology Journal. He died about a year and a half ago, in Texas. He retired there to play golf. His son is a professional golfer, teaches golf at the golf course there in Austin.

TB: So Mel was replaced by?

DG: Bill Swanson came along. But, Dave Mielke took over.

TB: I see.

DG: Bill Davis is the other person who's extremely helpful. Dave ended up doing more of the evaluations up there in Jackson, and I was doing less, having become involved in the alcohol and drug abuse area, and also, in the poverty area while teaching also medical students.

TB: When you say you got involved in the poverty area, what do you really mean? What did you do?

DG: Well, it was a free clinic that I started in the Fisher project and working with children in the Treme area, getting those with the high absentee rate to school. The Fisher project work went on for about four or five years, and we provided free general medical service there. They ended up getting a medical clinic established there, and so, we were able to leave. I felt like we had done our job, and now, they had a state clinic settled there that would take over the medical responsibility for the area. I had seen about two or three thousand patients in the Veterans Administration program, over ten thousand in the state program, over a course of about thirty years. I'd been the only the psychiatrist in the Southern state program in Substance Abuse, and I was the only doctor for a while, until we got an internist to help us out in the clinic. But I had no physician on my unit at the hospital in Mandeville, except myself, part-time, so, we saw this tremendous number of patients that I had the opportunity to treat and get involved with. I'm always running into them wherever I go. Without naming restaurants, there are one or two restaurants where I go, where about one-third of the staff were patients of mine at one time or another. So, it's a very interesting experience, to say the least. In fact, I have a cute story to tell you. This involves Dave Mielke and me. Dave and I, while we were working together, running the psychopharmacology research unit, every now and then would occasionally have dinner at Antoine's Restaurant in New Orleans. Also, when we had guests in town, we sometimes would go there. Sometimes Dave would take a guest; sometimes I would take a guest, sort of share the responsibilities, so it wouldn't be any more of a burden to treat the guests than it was. So, this waiter knew us very, very well, and the waiter had also been a patient of mine, in the alcohol and drug unit. And, he'd done well. He had been sober now for about ten years, or so, and had been working at Antoine's for about forty-five or fifty years, as a waiter. Anyway, one Monday, we found out that he'd had a stroke and they put him in Tulane Medical Center, so Dave Mielke and I went over to visit him. I thought he was comatose when I looked at him and I stuck him with a pin a little bit; I didn't want to stick him too much, and he didn't respond and his reflexes were very hypoactive. And, I thought, oh, my God, this doesn't look good at all. So, Dave was standing on one side of the bed and I was standing on the other side of the bed, and I said to Dave, "Gee, who are we going to get as a waiter tonight, who can we get now?" And, suddenly, now this is the

truth, suddenly, this fellow sat up and he said, "What are you talking about"? It must have been an ischemic episode, not the real thing, not a stroke. He said, "I'm still your waiter." So, I've had some fun, off and on, with patients like that. Want, another good story?

TB: Yes, please.

DG: OK, this is a true story. It doesn't sound true, but I had this bipolar patient, a shoe salesman who was an alcoholic. This was at an ACNP meeting in the seventies. I had a paper to present at one of the group meetings on the next day after I arrived by plane. My wife was going to come with me. The day we were supposed to leave, our kitchen burns down from a grease fire, so, she had to stay behind to take care of the insurance, but I had to go, because I had this paper to present the next day. So, when I was taking a shower that night in the hotel, the phone rang. My wife gets on the phone. She says, "Where are the insurance papers? I can't find them." So, I got out of the shower thinking, about where the insurance papers are; the operator gets on the phone and she says, Dr. Gallant, you have an emergency phone call from the States. It's one of your patients. So, my wife, being a good doctor's wife, said, "I'll hang up and you call me back later." So, she hangs up. This patient, this bipolar patient, who relapsed, and is drinking, and he's drunk, gets on the phone. He was a shoe salesman, and he says in his slurred speech, "Dr. Gallant how can I thank you? You've cured me and I've been able to sell three thousand pairs of shoes this week." And, I said, "Oh, my God." I got so upset, so aggravated that I hung up the phone. I had a bar of soap with me and I flushed it in the toilet bowl instead of putting it back of the shower. I was so turned around. So, sometimes, these situations were not that funny at the time, you know. There's nothing worse than a bipolar patient, who relapses on alcohol, as far as the physician is concerned. I mean, they can drive you nuts, unbelievable. And, I've had a number of incidents like that over the years. If you live long enough; you've had a good number of unusual as well as humorous experiences.

TB: You served on many committees during your career.

DG: Well, the FDA, Psychopharmacology Drug Advisory Committee; that was an excellent learning experience. That was very good. Actually, one of our former residents, Linda Kessler, who worked with the FDA asked me if I would join their committee.. She's now in private practice in Washington, and in fact, her daughter, came to be one of my Tulane medical students. That's when you know you're getting old. Well, anyway, at that time, being on the FDA committee was

really educational. I had one time when I really got stuck with something there. That was, beside that alprazolam (Xanax) incident, I was rotated to be one of the advisors sitting as the Chairman of that meeting that day. It turned out to be my bad luck to be the Chairman of the committee to evaluate LSD that was brought up to get approved by FDA as an investigational drug. And, without mentioning any names, it was a former ECDEU person, who brought his patients from his alcoholism unit in Maryland. And, he had his patients parade before our committee, each one, who had taken LSD, raving how wonderful it was and how the drug cured them of their alcoholism, but his data was inadequate. I had to sit there and moderate this meeting. He had no control data, no objective evaluations, and he wanted us to consider it as an investigational drug for controlled research. And that whole day, I was with all of his patients, who had been high on LSD, telling me that this drug should be approved to treat alcoholism. So, that was a learning experience, but it wasn't a very happy one for us. It was a daylong session that was totally a waste. There's also another story I can tell you about LSD, when I almost got thrown in jail. This took place here, in New Orleans. There was a fellow in the French Quarter that was caught with about 3,000 tablets of LSD on him, pink tablets, and about \$5,000 in cash. He claimed that he was a spiritual leader and that he was a religious leader for a religion called, the "League for Spiritual Discovery" using LSD. That, believe it or not, made it a constitutional case, due to religion. So, it ended up in the Federal courtroom, which is directly across the street from our alcoholism clinic. At that time, this also is ridiculous, our alcohol and drug clinic was located in the middle of the French Quarter, the 300 block of Chartres Street, right near the Royal Orleans Hotel. The Federal Courts were located directly across the street from us. The assistant district attorney, a woman, whom I dislike to this day, called me up and wanted me to testify, because we had done some research with LSD, which I didn't mention to you. I'll go back a little bit. We had, what was called, a "head clinic," here in New Orleans. This was during the "hippie days" and the Vietnam War days. The kids were transients. So we had a "head clinic," which is a free clinic that was running in the French Quarter. We had our medical students working there to treat the kids' medical and drug problems. So, we had a good supply of kids who had taken LSD to do some research with. So, Roberto Guerrero-Figueroa and I took forty of these kids, who had experimented with LSD twenty times or more. One group had flashbacks. It was two to three months after they stopped taking LSD, as far as we can tell. The other group had no flashbacks at all. Their use of other drugs seemed to

be about the same, so the only difference between the two groups was that one had flashbacks and one didn't. We did all-night sleep EEG's on them on our research unit over at Mandeville, where we had our lab research. And Roberto Figueroa, who was an excellent electrophysiologist, did the EEG readings, the all night data. Now, we didn't have computers set up then, so this was a time consuming experiment. In the end, we saw a much higher incidence of temporal lobe spiking from the scalp in the kids who had flashbacks, compared to those that didn't. It was about 60 percent vs. 15 percent, something like that. So, we had started publishing the data and I think it was printed in one of the EEG journals. Anyway, this assistant federal DA found out about it, so, she wanted me to testify in the courtroom case of The "League for Spiritual Discovery." So, I said, "Look, I can't do it right now. I have to go to Washington." Probably, it was an ECDEU meeting. I said, "We'll meet with you, now, in our office. I'll give you a couple of hours and I'll tell you all I know about LSD." She wanted to prove LSD caused fetal abnormalities. I couldn't give her that data, because we didn't have any data that said that. I did tell her about the flashbacks and our EEG data and I spent a couple of hours with her. When I reached Washington, my wife calls me on the phone and she says, "You have a subpoena to be in Federal Court on Wednesday." I said, "Wednesday." "I spent time with her. She promised me I wouldn't have to go to court; Wednesday afternoon is my married couples group therapy at the clinic and I have two groups to run anywhere from 1:00 till about 5:30 or quarter till 6:00." So, I said, "You know, I'm going to ignore the subpoena, because I gave her the time." So, that Wednesday afternoon, I was in the clinic. My 14 year-old daughter wanted to sit in with me in married couples group therapy to see what it was like, because she was thinking about becoming a psychiatric social worker. So, I asked the patients if it was alright and they said, fine. She was really a sharp kid. So she was sitting with me in the married-couples therapy that day and handling herself fairly comfortably. In the middle of group therapy, my secretary gets a phone call from the Federal Court, across the street, saying Dr. Gallant is supposed to be in the courtroom right now to testify in this court case. The court case is written up, by the way, in these red brochures, US Court of Appeals for the Fifth Circuit No. 72-2464. And, I said to the secretary, "No, you tell them that I've got this group and that I gave the deposition." She said, "The judge says he's going to send six Federal marshals across the street and carry you into the courtroom." I said, "Come on, now you're kidding" and hung up. And, I went back to doing group therapy. About twenty minutes later, my secretary calls me again, she

says, "They said if you're not there in five minutes, they're coming over here." I said, "Now, you're pulling my leg; don't joke around; come on, they're not coming here." Five minutes later, these six big hulking Federal marshals, and they were big, came in and they really picked me up, physically. My daughter is yelling, "Put my daddy down," and they carried me across the street to the Federal courtroom to testify in this case. I said, "Look, put me down, please, I've got to write some prescriptions for my patients." Some came from Lafayette, Louisiana. They did put me down and I wrote some prescriptions, and then, they escorted me, three on each side, across the street, my daughter following behind, yelling, "Let my daddy go." I walk into the courtroom. There are fifty hippies, probably hadn't bathed in five years. The courtroom was very smelly. They're sitting on the floor. They refuse to sit on the benches, because that would be recognizing the Federal government. The spiritual leader, this guy with this big long, red beard and shaggy red hair, was sitting there with his attorney, and yet, the judge is yelling at me, not at the kids sitting on the floor, yelling at me for not being there on time. When I try to explain that I gave a deposition, he wouldn't listen to a word I said. He said, "You just answer the questions. One more word out of you, I'll throw you in jail." OK. I'm sitting there testifying. Every time I testified with something that may be good for the defense, these kids started clapping. Every time I testified something negative, they'd boo me. The judge is banging away. It's like a B movie, comedy. The judge is banging away on the desk. My daughter is making faces at the judge for going after daddy, and I'm sitting there scared, now, that I'm going to get thrown in jail. I had so many things like that happen over the years. If you live long enough, you see a lot! Anyway, he didn't throw me in jail. The assistant DA won the case, but I never forgave her, and she wrote it up in such a way that she doesn't mention, in the case, my testimony as far as what happened in the courtroom. I was trying to tell the judge how she really lied and betrayed my confidence in her, and my time that I gave her.

TB: Did you do any other research with LSD?

DG: Well, that was the only time. I didn't work with LSD. I knew those who did. Heath and Russ Monroe worked with LSD when I was a medical student. What happened was that, I don't know who it was, but some government agency was concerned. This is 1952 or '53. They were concerned that the Chinese Communist were brainwashing some of our prisoners of war and they

had Ewen Cameron of Canada as one person evaluating LSD, without informed consent, by the way. Do you remember that?

TB: I was working with Cameron on that project.

DG: And Heath worked with a person down here, evaluating LSD and Russ Monroe did some of the work. And, they were doing it without real informed consent, because that was part of the idea. The whole thing was crazy. You know, part of the idea was you're not supposed to really know that you're getting LSD, if you're going to be brainwashed. So, they were only told they were getting some type of new drug, but there was no informed consent, to speak of. Well, this girl in my class volunteered for it. She ended up flipping out and had to be hospitalized for a couple of days. So, that was a terrible situation, as I recall, as far as LSD was concerned.

TB: During those years, people used LSD in the treatment of alcoholics. Did you use LSD in treatment?

DG: No, no. After I oversaw this FDA episode with the patient's parading in front of me, that they were into a religion with their LSD, I thought, this would not make for a good double-blind controlled study.

TB: Let us recapitulate briefly some of the events in your life. You moved to Tulane when you were eighteen.

DG: Seventeen going on eighteen.

TB: Started studying physics. Got a B.S., right?

DG: I got a B.S. in physics, and actually, at that point, I applied to medical school and was accepted. They thought my physics major was a little bit unusual. They liked to take people who had biology and chemistry, and they were leaning to accepting applicants with majors in chemistry, biology and psychology, but not physics. But I was made a member of Sigma Pi Sigma, the Honorary Physics Society. I think that helped me to get into Tulane; otherwise, I don't know if they would have evaluated my application in a favorable way, because they were really very hesitant to take Physics majors. They felt that physics majors were not that interested in medicine, per se. That was a feeling I had. And so, I really was concerned, when I applied, but it worked out okay.

TB: Your first paper was on dextro-amphetamine, if I remember well. When did you publish your last paper so far?

DG: This year. Well, not a paper, a chapter. Marc Galanter at NYU had asked me to do this chapter on alcoholism, on Treatment of Substance Abuse Disorders for the textbook that the APA puts out, and then, Gabbard, Dr. Gabbard, who's now in Texas asked me to modify my chapter, which I did for this 2001 book on the APA Treatment of Psychiatric Disorders. So, I'm still, occasionally, writing.

TB: What else did you publish recently?

DG: That's about it. I presented on Dual Diagnosis and that kind of material at USC, George Simpson's place, but I do very little of that now, because I feel like I'm out of the research mainstream. I do keep up with the reading, so I'm okay for doing reviews, but I'm certainly not doing any clinical investigations, any more.

TB: Did you do any research after you retired?

DG: In the VA Hospital, we were still doing various types of studies, as for example, the study we did on urine drug screens, immediate feedback vs. delayed feedback, as far as results are concerned, evaluating response, and so forth and published that data. So, I did a little bit later on, but not much.

TB: We talked about some of your collaborators. You trained many people during those years. Would you like to mention some by name?

DG: Well, actually, Steve Paul wrote his first paper with my supervision.

TB: Was Steve Paul your resident?

DG: No, he was a medical student. Steve wrote his first paper when he was a Tulane medical student, and he started residency up in Chicago, with Danny Freedman. He wrote two papers with us. He came to me and he asked me if he could try out one of the atropine-like compounds in our schizophrenic population and I told him to do a protocol for review and go right ahead. And then, Earl Usdin asked me to do a chapter on cardiac effects of various psychopharmacological compounds, and I asked him, "Look, I've got this medical student, who is very, very sharp. How about his doing the paper and being the first author? Of course, he's just a medical student and if he gets a lead authorship, even on a chapter, it'd be a nice start for him." So Earl Usdin said okay. The first time, I think they had said okay for a medical student to do a chapter in a book like that. I told Steve, "Look, why don't you write the chapter? You'll be lead author. I'll go over the paper with you to correct anything that should be corrected, but this is your baby and that's it." So, he did it, did a good job.

TB: Have you kept contact with him?

DG: Oh, yes. Actually, I was best man at his wedding. It was just Steve and his bride and me and my wife and daughter and the rabbi. They got married here in New Orleans. And then, of course, Chuck O'Brien was one of our residents. He got his MD and PhD in Pharmacology down here, and then, he started a residency down here. Peter Rabins, head of Geriatric Psychiatry and Vice-Chair at Johns Hopkins, also wrote his first paper with me when he was a medical student.

TB: Chuck was President of ACNP.

DG: Right, so, he, Peter Rabins, and Steve Paul were three of our successes, not bad, very good. Then, we had some other good people come out of here. I was just thinking of a person the other day. One of them is on the faculty over at Minnesota. We had a couple of people ended up as academic successes.

TB: What would you consider your most important contribution to the field?

DG: Well, I don't think I really made any significant contributions, when you really add things up. Actually, I think, in a way, the things I hold as my contribution really didn't make any impact, like the idea of doxepin in a controlled evaluation, being an anxiolytic back in 1969 or so. But, I feel that the times I served on committees, I think writing the Code of Principles, even though it's no longer applicable, was a very important thing. I really do. I think it was important for the ACNP to have one and it was important for me to do it; and I think it was a very valuable thing, at the time, particularly, in being able to get the entire membership, with the exception of one member, to vote for it. I thought that was a worthwhile accomplishment. Also, our controlled research with criminal alcoholics, first to report on the butyrophenone, trifluoperidol, my teaching awards, and the outstanding researchers I mentored. Steve Paul just wrote me that I am on the "top of his list for making his career possible."

TB: Any other contribution you would like to mention?

DG: I think my contribution to all of my patients was probably more important in the long run, the idea of being accessible by home phone and cell phone to them throughout all these years. To me, probably my main source of pride is having been always available to my patients twenty four hours a day, seven days a week, even though it involved thousands and thousands of patients. When I think about anything important, I always think about that.

TB: I think those clinics in the poverty areas that you established were a major contribution. DG: Yes, I felt good about that, although, there were some depressing episodes, you know. I mentioned the methadone patients, who didn't want to move out of the area, despite the fact that we would pay for their moving expenses. And, I think that the job we did with the children, taking them to school; things like that really, I think, affected me more in the long run than some of the drug studies I did, which didn't take any great intelligence. Although, I should emphasize that we designed our own protocols, did our own evaluations and statistics. The only thing the pharmaceutical firm did was give us the drug. Quite different at the present time!

TB: Have you ever been involved with geriatrics?

DG: Only in my getting old, as far as my own particular aging process is concerned. It's kind of funny, you know, I haven't thought about this in years. I did do some. This was back in about 1974 or '75. This internist in town started a small geriatric clinic on Tulane Avenue, right by the Broad Street Police Station. And, he asked me to consult over there with him, which I did for just one year, because I told him I'd help him get it started. And so, I did do it for a year, just a half a day a week, no big deal, just to get things started, evaluating the patients as far as organicity was concerned. That's why I was so happy that I started off with neurology. I really think that gave me an appreciation for the organic aspects, not just the psychiatric model. And then, after one year, I told him that was it. So, I did have that contact, which I'd forgotten.

TB: You received several awards and recognitions. You are a recipient of the Gold Achievement Award from the American Psychiatric Association.

DG: That was the best one, I think, because that was twenty-five years of work for which I received the Gold Achievement Award. We had to submit all of our research data that we had accomplished on the unit. We had to submit the number of patients we'd treated, the way we treated them, the whole program. I even enclosed my card with my home phone number and my work number to show them how we did it. In fact, the only time I ever cried at an academic award was during that particular presentation, because it was twenty-five years of work.

TB: Then you also received the Gloria P. Walsh award.

DG: That's a very nice award to get from the medical school because that's for the entire medical school, not just the department of psychiatry and neurology, the entire medical school for teacher of the year.

TB: You received that for teaching.

DG: Right. That's a nice award.

TB: You also had an award from the Association of Medical Educators. It was on substance abuse.

DG: Yeah, that was a nice award, because the year before they gave it to Charles Lieber. Charles Lieber is a man, whom I look up to tremendously, as far as research, is concerned. He got the award one year and I got it the next year. So, in my acceptance speech, which I had to give, and they published it in their journal, I talked more about Charles Lieber than I did about myself.

TB: Then, you had the Robert Lancaster award.

DG: Yes, the Lancaster award had a lot to do with my community work. I mean, they recognized some of the clinical research that I did, but also, they had heard about some of the work I did in the poverty area, the alcohol and drug abuse area with the state programs, and so forth, so that was more of a community situation. That was gratifying.

TB: Then, for fifteen years, every year, you had awards for outstanding teaching.

DG: Right, that's for outstanding teaching within that particular year of school, like the junior year, or something like that, so, it's not just as nice as the Gloria P. Walsh award, but it's a nice award because they have a banquet every year, and you get up, and they applaud. Very rewarding, with the students and the residents, I think it sort of keeps me on the young side, because I know what's going on with the younger generation. And, I know that any teaching time that I put in, is appreciated, particularly, nowadays, because of the way the medical school problems have developed as far as not getting paid for teaching hours. I think volunteer people like me are more valuable, nowadays, than they were, say, twenty or thirty years ago. In fact, I think we should end this interview with something Heinz Lehmann said. Before Heinz died, he was interviewed. I've forgotten what journal it was; maybe it was mentioned in the obituary in the Neuropsychopharmacology Journal, but he was working with New York State and involved in some type of teaching until very recently. And he said something like, I'm sort of paraphrasing here, I am not quoting, people over the age of 65 should pay to teach; not only should we teach for nothing but we should pay to teach. And I agree with that, because I get much more out of teaching than the students or the residents get.

TB: And these days you are reading a lot.

DG: I read anything that has a half way decent review. I use the New York Review of Books and the New York Times book section, the reader's section, and I also listen to my friends, listen to George Simpson. And, he's turned me on to a few good books and, then, I buy the books and, after I read them, I give them away. My wife reads them; I read them; we give them away, because I don't want to accumulate them. And, we pass them out to the residents, so forth. Sometimes the medical students appreciate them. And, I read fiction and non-fiction. It doesn't matter. And, I would say that books like *Regeneration*, Pat Barker's trilogy, those books are really fascinating, a combination of both psychiatry and a novelistic approach. In *Regeneration*, she talked about the case of the poets, Siegfried Sassoon and Wilfred Owen, the greatest war poet who ever lived, in my opinion. They had a type of post-traumatic stress disorder. They were treated by a psychologist who wrote the essentials up in *Lancet*, in 1919. He described his treatment approach in 1919. So, Pat Barker found out about this article in *Lancet*, and she took that article and made a novel, fantastic, really the best of the three books in the trilogy. I really recommend it.

TB: What do you think about the progress made in the field?

DG: I think psychopharmacology is really going in a beautiful direction. It's getting more and more specific with its drugs and they're hitting their targets much more accurately and the methods they have nowadays make the old time animal behavioral models looks so gross, it's pitiful. Yeah, I think it's fantastic.

TB: Are you pleased with developments on the clinical side?

DG: No, clinically, no. Of course, that goes for all of us, the HMO's, the PPO's, the whole thing is one big disgusting situation. You know, I used to give out my home phone number to everyone. And, when a doctor gives out his phone number, nowadays, the patients almost die from shock. Because of the time restrictions the psychiatrists, who work at the hospitals, most of what they do is dispensing drugs. There's very little relating going on now between the patient and the doctor, and you can't afford it financially, the way it works out. Let me tell you one story. Then, maybe, I should let you go. One of our outstanding residents, an excellent resident; he went out to Seattle, Washington, after residency. He really enjoyed psychiatry. He really enjoyed people. He enjoyed relating, was very good with psychotherapy and psychiatric drugs, and was going to be an outstanding psychiatrist. Well, he didn't have much money, so he signed up to work in an HMO. What he ended up doing is that the HMO decided that he'll be, mainly, a drug dispenser. If the

patient truly needs psychotherapy, he'll be seen by a social worker or a psychologist, which is less expensive for them to pay out. He had signed a three year contract. For three years, he was nothing but a medication dispenser. That kind of story really is terrible. So, I think, in medicine, in general, things are not the way they were years ago. I mean, you do find many good doctors, but they, as a group, don't have that much time to spend with their patients, and they're on a time basis, for the most part.

TB: What would you like to see happen in the future?

DG: What should happen in the future?

TB: What would you like to see?

DG: In the practice of medicine?

TB: Yes.

DG: I would like to see the physicians, in general, have the final say so as to how the patient should be treated, and not have so many administrators make medical decisions. I didn't tell you this, but I signed up with an Insurance evaluation advisory group, to find out the way they evaluate how long a patient should stay in the hospital, and this group works for the insurance companies, one that insures patients for hospitalization and so forth. These insurance companies use groups like these advisory groups to say, well, this patient is kept in the hospital too long. I just joined up, not to do the work, but I went to their meeting, as I was interested in learning. So, I spent my own money, making them think I was interested in joining, and I went up there to Madison, Wisconsin. This particular group has its base headquarters there. I sat in on their two day meeting and realized, after two days, that their purpose is never to go ahead and extend hospitalization for somebody with severe depression, who might need it, and has too many residual symptoms for discharge, but the whole purpose is to be able to cut down the hospitalization periods. And, some of the ways they did were quite obvious. Although the patients did require a little additional hospitalization, they found reasons to cut it down or not to approve the days. Well, having experienced that, in person, which was a good experience, I learned a little bit more that way. I felt that this is not the way medicine should go. To evaluate patient stay, first, there is the local carrier person, who is not a physician, but a nurse practitioner or someone like that. Then, it goes to this peer review, which has never even seen the patient. They're in Madison, Wisconsin or located in LA, but they're

not there with the patient and they're giving second opinions, if there's an appeal. So, that, to me, is totally unacceptable.

TB: Is there anything you would like to see in psychopharmacology and especially pharmacotherapy with psychotropics?

DG: Well, treatments are becoming more specific. Researchers are getting down to specific receptors and the genotype structures. For example, with the benzodiazepines, they're down to the alpha subunits of the receptor. That seems to be more specific. In Substance Abuse, they are down to the behavioral trait of impulsivity associated with dopamine-D₂ deficiency receptors in the nucleus accumbens, and even the possible Taq gene for possible treatment directions. This is the type of research that will be extending to all areas of psychiatric illness. More importantly, I would like to see the next presidential administration re-establish somewhat along the old-line ECDEU units with federal funding for a considerable number of independent academic, medical school institutions to do well-designed, reliable, honest, well-controlled drug studies with no impact or pressure from the pharmaceutical industry, whose only role should be innovating and supplying the new medications. Most importantly I, like all of us, would like to see that everyone should have free access to good medical care if they are unable to afford it.

TB: I think on this note we should conclude this interview with Dr. Donald Gallant. I would like to thank you, Don, for sharing all this information with us.

DG: You're welcome. It's been most enjoyable.

TB: Thank you.

21. GEORGE GARDOS

TB: This will be an interview with Dr. George Gardos²³ for the archives of the American College of Neuropsychopharmacology. It is December 9, 1993. We are at the annual meeting of the College in San Juan, Puerto Rico. I am Thomas Ban. Let us just start from the very beginning: where and when were you born? Say something about your background and so on.

GG: Thank you very much for asking me to do this. It is sort of a celebration. It reminds me of a few months ago, my father-in-law invited a lot of people to unveil his tombstone in the cemetery and he brought champagne and everyone drank to the event. It's very nice that I can do this while I'm still around here and working. Let me say a few things about myself.

I was born in Hungary, in 1938, and managed to get through the war. I stayed in Hungary and completed my high school and just when that happened, the 1956 revolution occurred. That gave a window of opportunity to people, who were shackled by the communist system, to get out. So, even though I just started medical school, in 1956, together with another quarter million or so Hungarians, I managed to get out to the West. I ended up in London, England where I had family. That is where I went to medical school at St. Bartholomew's Hospital, which is part of the University of London. That is where I got my medical degree, in 1962. Interestingly, while in medical school, I had practically no exposure to psychiatry, which was a deficiency of the English system then, and probably of medical curricula elsewhere, as well, in those years. I recall walking up to the common room in the hospital where I would relax and play cards, to pass a lab of a Dr. Michael Pare, who was doing some funny work. It was several years later that I discovered that he was doing pioneering work with MAO inhibitors. The other funny memory that I have is that there was a pharmacology exam that I would have done OK on, if on the oral exam I hadn't been asked whether I heard of chlorpromazine. I never heard of it and had absolutely no idea what it was for. The examiner explained it to me and I nodded wisely. Then, I forgot all about it.

After I graduated from med school, I spent a year in Rhodesia trying to figure out which way I was going. I was the assistant to the neurosurgeon, Lawrence Levy, there. He was the first

²³ George Gardos was born in Budapest, Hungary, in 1938. He completed his medical training at St. Bartholomew's Hospital, University of London and his residency in psychiatry at Boston Sate Hospital. He was interviewed in San Juan, Puerto Rico on December 9, 2003.

important influence on my research career. He was very busy with his practice, but he was very interested in doing a little bit of research, some animal experiments. And he encouraged me to make clinical observations and follow them up if warranted. My first paper was published while I was still in Rhodesia, which is now called Zimbabwe. It had to do with two cases of subdural hematoma resulting from anticoagulant therapy. My chief encouraged me to write it up and helped me with it. So, it got published in the Central African Journal of Medicine. That was a very important influence; it taught me the importance of making clinical observations and if they were of value to communicate my observations in a publication. I also learned in Rhodesia that I was not cut out for surgery, whatsoever. From Rhodesia I came to the United States as a graduate student in psychology. I had, at the time, interest in mental health and I ended up in psychiatry through the back door. As a graduate student in experimental psychology I got my master's degree.

TB: What was your master's thesis on?

GG: My thesis dealt with the auditory environment, with ability to rearrange the auditory environment. The subjects in my experiments were wearing "artificial ears," which deflected the direction of sound so that it appeared to be coming from the side, creating a conflict in determining where the sound came from. It was a way of studying plasticity in the nervous system.

TB: When was this?

GG: This was, in 1965, and unfortunately my student visa was about to expire. So, I was headed back to England, but before leaving to the UK, I took a little trip to the West Coast to look around. Then upon returning from the West Coast, just before starting to pack, I found out about a job opportunity for a research associate at the Massachusetts Mental Health Center with Al DiMascio. He was the next major influence in my career. He interviewed me and we hit it off well. He was very helpful. He helped me change my visa so I could stay and I started to work in his lab at the Massachusetts Mental Health Center.

TB: Could you say something about the Massachusetts Mental Health Center in the mid-1960s?

GG: The Massachusetts Mental Health Center, in 1965, was a vibrant, very exciting place, but also, a place in turmoil, because on one side of the building were the wards, where the psychiatrists were in charge and anything but psychotherapy was frowned upon, and on the other side of the building, were the research laboratories where exciting research took place. Some of the

psychoanalysts on the clinical side were true believers. The research lab was run by Dick Shader and Al DiMascio and had young energetic psychiatrists like Carl Salzman and Roger Meyer. They did exciting work. I got involved in trials with benzodiazepines in symptomatic volunteers. I did a study comparing oxazepam and chlordiazepoxide in symptomatic volunteers studying the effect of these drugs on hostility, finding a paradoxical effect. Subjects given chlordiazepoxide showed increased hostility, whereas subjects given oxazepam did not. Al DiMascio was my first mentor. He was incredibly energetic, bright, and likable. He was also a true believer in the future of psychopharmacology. In some ways, he was very much ahead of his time. He had gotten a computer, already in those years, and was learning to analyze data on it because he knew, back then, that computers were going to be the thing in the future.

It didn't take me long to realize that without a valid medical degree in the USA, I had only limited options in work and I decided to take the plunge and started my residency at the Boston State Hospital, where Milton Greenblatt just initiated a number of pioneering community programs and started to empty the wards in this hospital. It didn't take me long to realize that psychopharmacology was the future. Psychotherapy for schizophrenics didn't seem to do much for the patients. So, I thought I would need to learn more about psychopharmacology and using medications.

TB: So, you had your residency in psychiatry at the Boston State Hospital?

GG: I went to the Beth Israel Hospital in my third year for more traditional training. It was useful because at Beth Israel, I got exposed to more verbal and educated patients than at Boston State. After Beth Israel, I returned Boston State and stayed for the next 8 years or so. My main reason for staying was the arrival of Jonathan Cole, who took over as superintendent of the Hospital from Greenblatt and created a very exciting atmosphere. He did the same there, as he did on the national level, before, as head of the Psychopharmacology Service Center of the NIMH; he attracted people with interesting ideas and helped everyone to do research. He helped people to get funding and supervised them. He attracted a number of researchers and I worked with quite a few. Eventually, there was a plan for a research institute to be built there.

TB: Could you say something about your research?

GG: As to my own work, I started to be involved in research under Jonathan Cole's mentorship, and I did a number of studies with antipsychotics. I was interested in refining the clinical use of

antipsychotics; in optimizing the use of psychotropic drugs and especially of antipsychotics. I did some studies to assess dose-effect relationships. I felt that the dosage variable was not sufficiently appreciated, and found that in low doses, some drugs had completely different effects than in high doses. I noticed that small doses of neuroleptics could be used for conditions other than psychosis, e.g., for anxiety and depression. I did a study on thiothixene and found that in low dose it had some antidepressant effect. We did notice some improvement in mood and energy. We used scales for measuring changes, like the BPRS, as well as measures like participation in rehab programs, and found that patients on low doses were more likely to participate in these programs. I studied new drugs developed for the treatment of anxiety. I did a pilot study with propranolol in high doses, in schizophrenia, and found that the substance was not safe to administer in high doses. I did an intriguing study on a medication called Thorastal, which was a combination of Thorazine (chlorpromazine) and Stelazine (trifluoperazine). This was a comparison study with the components of the combination, and what was bizarre was that our findings did not even show difference in sedation between chlorpromazine and trifluoperazine which clinically did not make any sense. But then findings of research studies do not always jive with what one sees in the clinic. Boston State in the 1970s was an exciting place, and some of our studies were directed at assessing how discharged patients fared. I did some work with family care patients and studied their social adjustment.

TB: Any other research projects you would like to talk about?

GG: We did a study way back at Boston State on clozapine. We had positive findings but we didn't see anything dramatic. Jonathan Cole went over to McLean Hospital from Boston State, in the late 1970s. I joined him, and stayed with him for years, while I continued my work part-time at Boston State. Jonathan Cole, besides being an eminent researcher, was also a superb clinician. He had tremendous communication skills. In the late 1970s, when the literature was somewhat dogmatic with respect to mono-therapy, I saw Jonathan's patients walking out of his office with three or four prescriptions and they did well. The major research program I was involved in at McLean was our tardive dyskinesia (TD) study. It involved close to 200 patients who developed TD. We followed them for a long time, up to 15 years. This study enabled us to get data on epidemiology, risks factors, course, and treatments. To summarize our findings, we came to the conclusion that tardive dyskinesia really was not as malignant and horrible as usually perceived.

After five or ten years, patients managed well and got better, rather than worse. The situation about TD changed radically with the arrival of the atypical antipsychotics in the mid-1990s, of which, clozapine was the first, and remains the gold standard.

TB: Would you like to comment on your experience with atypical antipsychotics?

GG: There are still major questions about the efficacy of atypicals. They don't seem to be as effective in the office, as one would like to see. I combine them with more potent dopamine-D₂ blockers to get a better response.

TB: Could you tell us something about some of your other projects in TD?

GG: I had done a long term follow-up study with Daniel Casey, in Hungary, where TD seemed to be less prevalent than here. This was an interesting study. I became impressed with the particular clinic where it was done because they used a great deal of drug combinations. They didn't seem to be more or less effective than mono-therapy. The clinical findings with antipsychotics were comparable in Hungary and the USA.

TB: When did you start your private practice?

GG: I started private practice, on a part-time basis, in the 1980s, and I am still seeing many of my old patients. It is interesting to age with them. I have patients that I have followed for 25 or 30 years.

TB: Is there anything else you would like to add about your research or research in psychopharmacology in general?

GG: I am, in some ways, a dinosaur by insisting on clinical science. In terms of my practice, I think the appearance of Prozac (fluoxetine) was a watershed. It just made my practice with drugs almost 50% easier overnight. I had a wonderful feeling that I could now give a medication to a patient and I didn't have to worry about getting called about side effects at night. Most of my patients, for whom I prescribed the substance, got better and liked to stay on the drug. Most patients today come with a drug history and that, of course, dictates the choice of drug to be used in treatment. Most psychiatric diseases are chronic, and they are controlled, but not cured with drugs.

TB: When were you elected a member of ACNP?

GG: In 1987. I am honored to be a member of ACNP and I look forward attending the Annual Meetings. I think this organization has done tremendous work for science and patients.

TB: Thank you, George.

GG: Thank you, Tom, very much.

22. SAMUEL GERSHON

TB: We are at the 38th annual meeting of the American College of Neuropsychopharmacology in Acapulco, Mexico. It is December 15, 1999, and I will be interviewing Dr. Sam Gershon²⁴ for the Archives of the American College of Neuropsychopharmacology. I'm Thomas Ban. So, Sam, let's start from the very beginning. Where were you born, brought up? If you could say something about your early interests, education, and how you got involved in neuropsychopharmacology.

SG: We'll start when I was born. It was in 1927, and that event was in Poland. Then, in 1929, we came to Australia and I had my education, including medical school, in Sydney, Australia. After that, I went for a psychiatric residency to Melbourne, and then towards the end of that residency, I had a fellowship in the physiology-pharmacology department at the University of Melbourne. Essentially, I continued in the various activities in that department till the end of my residency in 1956. And then, I went full time to the Department of Pharmacology at the University of Melbourne, and essentially stayed there till, pretty much, I left for the first time to the United States, in 1959. Before I left, I was the acting chairman of the department of pharmacology. Then I went to the University of Michigan in Ann Arbor on a Pfizer Fellowship and I spent a year there.

TB: What did you do after that year?

SG: I went back to Australia, to the Department of Pharmacology, in Melbourne. I stayed a year there, and then I returned to the United States to work in the Missouri Institute of Psychiatry in St. Louis for a couple of years. Then I went to New York University (NYU), and stayed there for seventeen years.

TB: You've jumped over several years of your activities in Australia. Could you talk about what you did in those years?

SG: During those years I was a resident in psychiatry. I had a mentor at the University of Melbourne, Dr. Trautner, who had started the first large study of lithium after the publication of

²⁴ Samuel Gershon was born in Lodz, Poland in 1927 and received a medical degree from the University of Sydney in 1950. He trained in psychiatry at the University of Melbourne and then turned to pharmacology, becoming the acting head of the department at Melbourne, in 1961. In 1963, he immigrated to the United States, taking a post at the Missouri Institute of Psychiatry. In 1965, he became director of the Neuropsychopharmacology Research Unit of New York University, spent the years from 1979 to 1988 as director of the Lafayette Clinic and chairman of psychiatry at Wayne State University, and from 1988 to 1995 as Associate Vice Chancellor for Research at the University of Pittsburgh. Currently he is Vice Chairman of Academic Affairs in the department of psychiatry at the University of Miami. He was interviewed in Acapulco, Mexico on December 15, 1999.

Cade. Cade's publication was in 1949 and Trautner, as soon as the beginning of 1950, started a large clinical trial of lithium. He studied one hundred psychiatric subjects, more than anybody had before or for a long time after. He was also first to introduce the use of plasma lithium assays. It was possible for him to do that because about a year before, Dr. Victor Wynn at the University of Melbourne published on the use of flame photometry to assay electrolytes, including lithium. So, in all the patients he studied and published on in 1951, he had done plasma lithium assays. In his publication, Trautner noted that one should monitor lithium levels to prevent potential toxicity. And that was an enormous advance for the clinical use of lithium. Cade had never used plasma lithium monitoring; he felt that adequate clinical observations were sufficient. About the same time, two important events relevant to lithium treatment took place. First, in 1949, in the United States, many people died from lithium poisoning when lithium chloride was marketed as a substitute for sodium chloride for treating patients with hypertension. Then, in 1951, Trautner pointed out that monitoring lithium levels indicated a therapeutic window of the drug. And he, pretty much, set the window the way it's always been for fifty years, from 0.6 mEq/L to 1.2 mEq/L. So, very early on after Cade's paper was published, Trautner's paper appeared and provided some essential information on how lithium should be used. Undoubtedly it was Cade who made the initial observation on the therapeutic effects of lithium.

But it was Trautner's work that made possible the broad clinical use of lithium. Trautner also highlighted that the action of lithium is pretty much restricted to its efficacy in typical mania. He was supportive of the specificity of lithium for mania, an issue that has been debated during the past fifty years and has remained pretty much unresolved. Following Trautner's first report, we conducted a series of other lithium studies. One of these studies, published in 1955, dealt with the teratology of lithium. It is interesting that at this annual meeting, Dr. Manji referred to some of the teratological findings we had with lithium on tadpoles. In fact, all we found was a high rate of embryonic absorption in frogs; and as far as we could tell, lithium had an effect on embryogenesis but there was no teratology. Today, in the light of some later reports in humans, the teratology of lithium is clearer. The purported increase in cardiac abnormality did not seem to be supported by later reports, which indicated that the incidence of cardiac abnormalities with lithium is within the statistical distribution of the general population. Still, some teratological findings with lithium might be real.

TB: Did you participate in establishing the therapeutic window of lithium?

SG: Yes. We didn't go around and establish the therapeutic window. We essentially said that's what we thought it was. The idea that we should go around and establish it in controlled studies, back in the early 1950s, never entered our mind. There was no funding to ever contemplate such a study in Australia.

TB: Did you do any other clinical research with lithium?

SG: Oh yes, we did many studies with lithium after the first one. In one of these studies, we found increased retention of the lithium ion in the manic phase, and increased excretion of it when mania was resolved, followed by homeostasis. We published these findings, in 1955, with the title, "The excretion and retention of ingested lithium and its effect on the ionic balance of man," in the *Medical Journal of Australia*. I was also involved in the teratology paper and in another paper with lithium, which didn't have lithium in the title. It was a paper on the pharmacological treatment of shock dependency. We had bipolar patients and they were on maintenance ECT; we gave them lithium, not just for the episode, but also for prophylaxis, to replace ECT, and that's where the title came from. We could, essentially, treat shock dependency prophylactically by giving lithium for the long-term.

TB: Any other studies?

SG: Yes.

TB: Could you say something about your other studies with lithium while in Melbourne?

SG: There were a whole lot of lithium studies that followed the first one. The other ones were related to findings that tended to indicate that we might have to limit the clinical indications for lithium. We thought first that it would be indicated for recurrent episodic psychotic activity. And that included what, some years later, Perris referred to as cycloid psychosis. The central thing we found with lithium is that its efficacy is restricted to pure bipolar disease, to the so-called typical manic depressive disorder, as described in British texts.

TB: What other research did you do besides lithium in Australia?

SG: I did a whole lot of other research in Melbourne in the Department of Pharmacology. I got involved in looking at pharmacological antagonists to morphine, and we developed synthetic compounds in the department for this purpose. We tried them in animal models, for example, in dogs, because the dog responds with dose-dependent sedation to morphine. We actually developed

a series of amiphenazole-like compounds, which were antagonists to morphine. We also developed some indole alkaloids that were also antagonists. Another morphine antagonist we identified was succinic acid. It's a dramatic antagonist to morphine-induced sedation and morphine coma. The last substance we tested in our animal model was THA, tetrahydroaminoacridane.

TB: Could you elaborate on your findings with THA?

SG: Well, we found that it was a morphine antagonist. It is clearly a cholinesterase inhibitor.

In the last ten years or so, the focus of research with THA was in the treatment of Alzheimer's dementia, based mainly on its cholinesterase inhibiting properties. At the time we worked with THA we also had a series of atropinergic agents available which could produce aberrant behavioral states in dogs and induce atropine psychosis and coma in humans. The interesting finding with THA was that it was a potent antagonist to both morphine-induced sedation and atropine-induced aberrant behavioral states. It was also a potent antagonist to imipramine and amitriptyline delirium; and was used therapeutically for these indications. Then later on, in 1960, we developed other aspects of its utility when we found that similar to succinic acid, it has a general alerting effect in many CNS depressed states.

TB: Could you elaborate on this research?

SG: Well, this research goes back to 1959, when I went to the University of Michigan to work in the – at the time famous – schizophrenia and psychopharmacology research project, headed by Ralph W. Gerard, at Ann Arbor. Gerard was a neurophysiologist but he had ideas about how one could dissect schizophrenia by various basic science approaches. Of course, it didn't work out that way, but it provided a very remarkable opportunity to do other research. What we were involved in was the use of chemical models for psychiatric disorders. We had available at that time a psychotogen, called Ditrane, which was an anticholinergic agent that produced in dogs a hyperactive disturbed behavioral state. Based on my previous research with atropinergic agents in Australia, we administered THA to dogs and found that it antagonized the Ditrane-induced state and restored animals to normal behavior. So, we had an anticholinergic paradigm of what could be considered grossly aberrant behavior, and we had an antagonist. Ditrane produced a psychopathological state where the individuals would have hallucinations, delusions, and some disorientation, and its effect could be counteracted with the administration of THA. At the same time, other people were using phencyclidine, Sernyl, to induce a psychotogenic model state. We

also had the opportunity to study Sernyl-induced psychotogenic model states. THA had an inconsistent antagonistic effect of phencyclidine-induced psychopathology.

We had studied in Australia a series of yohimbine alkaloids, including yohimbine indole alkaloids, harmine derivatives, and ibogaine derivatives, in dogs, and found that all indole alkaloids antagonized morphine-induced sedation and coma, and also the psychotogenic states induced by anticholinergics. So when I got to the U.S., I had the opportunity of taking the yohimbine research from the animal model into the human and testing whether yohimbine has anxiogenic effects. After a series of experiments in animals, we injected yohimbine intravenously into humans and we saw a dose-dependent anxiety state produced with all of the physiological concomitants. By increasing the dose of yohimbine, we could produce panic. In both dogs and humans, there was an increase in blood pressure and pulse rate with all of the other autonomic effects that a patient with anxiety would have, such as sweating, etc. We had also shown that any of the anxiolytics available at the time would control this yohimbine-induced anxiety and panic state in humans. An interesting finding was that tricyclic antidepressants aggravated the anxiety. We did a lot of other experiments with this anxiogenic model, and many years later, the group at Yale used the yohimbine model as a sensitizer in a whole lot of studies of panic states.

TB: If I understood you correctly, all this research started in Australia in animals?

SG: All of this started there. None of the indole stuff was done in Australia in humans. It was all done in animals. I was involved between Australia and the U.S. in the development of a number of agents that could be used as chemically induced models of schizophrenic-like states, and yohimbine, as a model of anxiety and panic. I was also involved in the development of antagonists to all these agents.

TB: Was all your research in Australia done in the department of pharmacology, after you completed your residency in psychiatry.

SG: Yes. Actually psychiatry at the time was not a big thing in Australia. The departmental chairman in Sydney was a gentleman called Wolfgang Siegfried Dawson, who had written a textbook of psychiatry, which would fit into your vest-pocket. That was the size of his textbook in psychiatry. In Melbourne, there was no chairman of psychiatry at that time. There were chiefs of psychiatry divisions at the teaching hospitals.

TB: I assume this was before Brian Davis became chairman.

SG: Oh, yes.

TB: Did you do any clinical work in psychiatry, while you were in the Department of Pharmacology in Melbourne?

SG: I had an appointment as a consultant psychiatrist to two of the teaching hospitals.

TB: You went to the States for a year. Was your appointment at Ann Arbor in the department of psychiatry?

SG: I was in Michigan from 1959 to 1960, and during that year, I was doing research in a schizophrenia and psychopharmacology project that Ralph Gerard was running. It was a project that was funded by the NIMH through Jonathan Cole's division. Actually, it was during that time that I met Jonathan Cole for the first time, when he site visited our program that he funded.

TB: When you say Jonathan Cole's division at NIMH, are you referring to the Psychopharmacology Service Center?

SG: Right. He had with him, at the site visit in '59, Gerry Klerman and Reese Jones. So, I met Jonathan Cole and these other folks. And Jonathan was to become an important contact for me from then on, even after I went back to Australia for a year.

TB: What did you do during the year you were back in Australia?

SG: On my return to Australia in 1960, Dr. Shaw and I undertook a study on the effect of organo-phosphorus insecticides, which are non-reversible cholinesterase inhibitors that some scientists and farmers are exposed to. We found that some people in contact with such insecticides developed either a depressive or a schizophreniform psychiatric disorder. I was back in Australia only for a year, because on Jonathan Cole's suggestion, the people at the Missouri Institute of Psychiatry, in St. Louis, got in touch with me and invited me to join them.

TB: Was it George Ulett who invited you?

SG: George Ulett was there and also Max Fink; they were running the show and I joined them.

TB: Could you tell us something about the place and also about the research you did while there?

SG: It was a remarkable place. It was one of the premier physical facilities available for psychiatric research in the United States. George Ulett had an enormous vision for creating that research institute. Have you ever visited the place? Heinz Lehmann was there many times.

TB: I did visit, but later on.

SG: It was a remarkable place. I had 150 dedicated research beds when I got there. I had also the opportunity of becoming involved in finalizing the building. All of the animal laboratories were state of the art facilities. I stayed there for two years, approximately, and that gave me an opportunity to do a whole lot of animal work and a whole lot of clinical studies, as well. I also had the opportunity to do electroencephalographic (EEG) evaluations with Max Fink and Turan Itil and study the central nervous system effects of the agents I worked with in Australia. So we could clearly document in a series of studies the dramatic slowing of the EEG induced by anticholinergic drugs in human. We administered Ditrane and documented that it produced similar changes in the EEG which are seen in patients with neurological deficit, brain injury, and alcoholics with cognitive deficit. We also documented the antagonistic effect of THA to Ditrane on the EEG, and noted that those patients with neurological damage get cognitive deficit after the administration of lower doses of the drug.

TB: So your later work with cholinesterase inhibitors was based on your research in animals in Melbourne and research in humans in St. Louis?

SG: Oh, yes. THA was the first cholinesterase inhibitor I worked with and we had our first studies in animals with THA in the late 1950s and early 1960s. It was many years later that based on our early research, THA was tried in the treatment of Alzheimer's dementia.

TB: So, it was your finding in St. Louis that THA counteracts anticholinergic-induced EEG changes combined with clinical observations that the substance could counteract the cognitive deficit produced by anticholinergic drugs that led to the research with cholinesterase inhibitors in Alzheimer's dementia. How long did you stay in St. Louis?

SG: I was there about two years.

TB: Did you do any other research while there?

SG: There was a lot of activity in St. Louis; we had a very good group there, a bunch of laboratory pharmacologists and a bunch of clinicians. We had neuropsychologists and we had visiting psychiatrists that would come from other countries and work on our various projects. It was a very stimulating environment. And, as you know, later on, due to whatever political difficulties existed within the state of Missouri, it essentially died.

TB: Didn't this happen after you left?

SG: I left before it died.

TB: You left for NYU?

SG: Right.

TB: How did you get to NYU?

SG: I got a job there. Actually Arnie Friedhoff was responsible for recruiting me to NYU. Arnie had a very active program in psychopharmacology there, both preclinical and clinical. And, with his help, we had the opportunity of trying to replicate a combined pre-clinical and clinical program in psychopharmacology. I think I got there in about 1963. It was a great setting; it provided all sorts of opportunities.

TB: Could you talk about your research at NYU?

SG: We had the opportunity there of having a research ward. We had laboratories and we had the opportunity of recruiting young research fellows into a psychopharmacology research unit in the department of psychiatry, with a lot of support from Arnie Friedhoff, and the chairman at the time, who was Sam Wortis, Joe Wortis' relative, not his brother. Sam Wortis was never an important figure in psychopharmacology, himself, but he was sort of a main support individual for biological research in psychiatry in his department. I think it's not known to many people, but he was a very important figure, nationally as well, in supporting biological psychiatry in many ways, influenced in that direction by Arnie Friedhoff.

TB: Could you say something about the research in your unit at NYU?

SG: Well, I was there for a long time from 1963 until about 1980. That's almost seventeen years and, golly, we had a whole bunch of people. We managed to attract a lot of young research fellows, who really have all developed into very successful individuals. And I think it's very important to stress the value of the opportunity to mentor young people. It's really something that should be addressed in some form or way in a setting like the ACNP. They do have many fellowships in the ACNP for various groups, but that's not exactly the same as close physical mentoring, in one's department or division or facility. That seems to be the essential component. We started, in New York, a lithium program and a lithium clinic, at the time that Baron Shopsin joined. And we developed a very large program in bipolar disorders. Out of that program came a lot of work dealing with the specificity of lithium for the diagnostic entity of bipolar disorder; Baron Shopsin, together with others in the group, did a series of studies looking at lithium vs. neuroleptics vs. a control group in the treatment of schizoaffective disorder and schizophrenia vs. mania. The other

person that joined us and worked in the same area of research was Gordon Johnson from Australia. He spent several years with us as a Fellow. Our research tended to support the idea that lithium was effective in controlled studies against a reference drug in mania. It was clearly better than placebo. Chlorpromazine was the active reference drug at the time. It was certainly effective and had a faster onset of behavioral control in mania, but the opinion that resulted from those studies was that lithium had a much more significant effect on the core pathology than chlorpromazine did and patients could be discharged at about the same time, but their functional level appeared to be more intact with lithium than with the neuroleptic. These were the findings in the studies conducted by Johnson and Shopsin in mania.

Then, studies were done in a schizophrenia group and a schizoaffective group and there it appeared fairly clearly that in the schizoaffective group, lithium was dramatically less effective than the neuroleptic, either chlorpromazine or Haldol (haloperidol). These findings tended to support the specificity of lithium in the treatment of mania. In fact, not only was lithium less effective than neuroleptics, but it appeared to increase pathology in the schizophrenic and the schizoaffective groups. Baron Shopsin then led a series of additional studies with lithium, where we pursued the finding that lithium has very major effects on thyroid function and caused hypothyroidism. And then, a whole lot of other research was conducted with endocrinologists to find out how lithium was producing hypothyroidism.

TB: Were these some of the earliest findings on the effects of lithium on the thyroid?

SG: I can't say that we were the first or the second in showing the effects of lithium on the thyroid, but these findings were early on. Another very dramatic finding was that lithium produced leukocytosis. We published it in about 1970. It hung around as a potential harbinger of some horrible hematological disease, until these patients were followed up for longer periods of time, and other investigators in Europe, especially Schou and others, could assure everybody that lithium has no serious hematological effects. Later on, it was found that one could use lithium induced leukocytosis in cancer chemotherapy, to increase white cell count that was depressed by chemotherapeutic agents for cancer. So, even if that was an adventitious finding, it was clearly, an important one. The actual mechanism of how lithium increases white cell count is unknown to this day. These research activities with lithium developed as a sort of separate research division from the other research activities we conducted with lithium at the same time. For example, we studied

the ratio of intracellular and extracellular lithium and the importance of this ratio in the clinical use of the substance. We also developed an assay for measuring lithium in the saliva, instead of the blood, and a statistic for translating the saliva value to the plasma value. Also, Gordon Johnson did a whole lot of EEG studies with lithium in bipolar disorder. He found that patients with cognitive or organic neurological damage were supersensitive to lithium's central nervous system adverse effects. He also correlated the lithium induced EEG changes with intracellular and extracellular ratio shifts of lithium. So we had a whole series of studies in our lithium program. We also had a schizophrenia research program with Burton Angrist.

TB: So you had a research program with lithium in bipolar disorder, and a research program in schizophrenia?

SG: We did have these programs, and we also started one of the early geriatric research programs, at a time when thinking about Alzheimer dementia must have been pretty naive, because the first funding support we had from NIMH for geriatric research was for a very large and very expensive study on hyperbaric oxygen in the treatment of senile dementia of the Alzheimer type. Once we knew that we were going to get that level of support in geriatric research, we had to recruit staff that would implement this very large and very expensive project. At NYU, we already had a hyperbaric chamber which was not used very much, so they were very happy for us to use it. At that time, I recruited Steve Ferris, who came as a neuropsychologist to the program, a bit later, Barry Reisberg, and later on, Mony DeLeon. All three are full professors now in the department of psychiatry. All three are now internationally recognized in the area of Alzheimer's research. And that was out of a mentoring experience; all three entered the field with no prior research experience in any area. I think this shows that all you need is bright people and a structure that permits intimate mentoring.

TB: You mentioned hyperbaric oxygen as one of the projects you had in your geriatric program. What did you find?

SG: It was clear at the end of this expensive exercise that hyperbaric oxygen was no better than placebo. But, it helped in establishing a very talented geriatric research group.

TB: What else did you do in your geriatric research program?

SG: That geriatric research program developed in many different areas, looking at potential therapeutic agents. And then, each of the people that I mentioned contributed to geriatric

psychiatry with their particular knowledge and expertise. Mony DeLeon has gone on to become a major figure in looking at changes in the morphology of brain nuclei in Alzheimer's disease using magnetic resonance imaging (MRI) and identified the targeted changes in the hippocampus. Barry Reisberg has gone on to describe the phenomenological aspects of deteriorating brain functions and developed scales for documenting this. And Steve Ferris has become a major figure in the psychological measurements of changes in dementia in geriatric patients. The program provided the infrastructure for looking at potential therapeutic agents. THA was the first compound to get FDA approval as an agent in the treatment of dementia. It was the old compound, THA, which had some minimal effect on the symptoms of these patients, but no matter how modest its effect was, it changed the climate and moved research in the treatment of diseases in the aged from studies which made no sense, like the one we did with hyperbaric oxygen, to studies that would test and could support hypotheses like the cholinergic deficit hypothesis, as one contributing factor to the development of Alzheimer's disease. Regardless of how minimal the effect of THA was, it changed our thinking in this area of research by turning attention on the possibility of trying to find drugs that would intervene with the process that leads to dementia. And that was very important, a major, major change in the watershed of looking at therapeutic concepts for this condition, heretofore considered completely untreatable.

TB: Was yours one of the first psychogeriatric units in the country?

SG: One of the early programs in the country was set up at NYU and the program has National Institute on Aging center support, till now. It was established early on and it has developed and grown enormously without me being there. It has done much better since I left.

TB: Could you say something about your program in schizophrenia?

SG: The schizophrenia program was quite diverse. We looked at lots of therapeutic agents, and we also looked at the concept whether there was a therapeutic window, a metabolic target with chlorpromazine in schizophrenia. Then we did quite a lot of research about metabolites of chlorpromazine that have therapeutic activity. We were the beneficiary of NIMH support for looking at plasma levels of chlorpromazine, its millions of metabolites, and their therapeutic activity. We had a laboratory developed to do chemical assays for these compounds and we had several years of support in looking at the effects of these metabolites and clinical outcome. Again, our first effort in this area of research was not revolutionary. But soon after we started our program

in schizophrenia, Burt Angrist came along out of a residency program, and he was interested in starting research in this area. He joined as a research fellow, and we were looking around for a potential project for him. Based on my prior work with chemically induced models, we discussed the possible value of a dopaminergic model. We were, at the time, in the early sixties. There was important work done on amphetamine and psychosis, psychosis in amphetamine users, published by that time. We decided with Burt Angrist to first do a survey of patients admitted with amphetamine psychosis. Burt had a superior sensitivity to clinical phenomenology, and he would then follow these patients, who were admitted through to their remission, and document phenomenological changes from the acute phases of the psychosis to clearing and remission. He documented what might have been known before, that hallucinations went first, and then delusions, and so on. He put the phenomenological changes on a very firm footing. Then, since with amphetamine we're not manipulating one but several transmitters, we carried out a whole series of experiments in which we had the opportunity of measuring metabolites of neurotransmitters on people who were admitted. Burt Angrist clearly showed that within a four to five day period, one could induce with amphetamine a psychosis that was not just a paranoid excited hyperactive state. You could produce a psychosis with negative symptoms as well. You could produce energy, and the whole clinical picture of schizophrenia. He raised the issue that this was, in truth, a very interesting analog of the disease itself, and then went along with many of the other hypotheses that supported the dopamine construct that was then the mainstay in the development of antipsychotic drugs. Then he took it further by looking at to what extent norepinephrine played a role vs. dopamine and its metabolites and tracked the whole sequence of events to essentially target dopamine as the primary guilty component in this development. That whole program with Burt involved fit in, very much, with work that Arvid Carlsson was doing on the dissociation between dopamine and norepinephrine. So, that was really a very profitable venture. And there were many other people that were involved in our schizophrenia program. One of them was John Rotrosen, who joined the group early on. He is professor of psychiatry now at NYU, and a member of the ACNP.

TB: Didn't you have also a program in depression?

SG: Yes, we had a program on depression. Some of the work in this program was done with the scientific input of Menek Goldstein, and that was very interesting. Of course, it raised again the

issue that there's not one culprit, but then maybe there is one that's more important than another. We did some experiments, in which Baron Shopsin was involved and a lot of other people, like Sherwin Wilk from Mount Sinai. So essentially, we treated endogenously depressed patients with either imipramine or a monoamine oxidase inhibitor, till there was a therapeutic response. Then all those patients that achieved a therapeutic response were assigned at random to either α -methylparatyrosine (AMPT) or parachlorophenylalanine (PCPA), thus inhibiting norepinephrine metabolism in one, and serotonin metabolism in the other. The dramatic effect simply was that the group, in which we inhibited norepinephrine stayed fine, whereas in the ones we inhibited serotonin, all relapsed within twenty-four to forty-eight hours. These findings, of course, were later confirmed by Aghajanian and De Montigny at Yale, doing neurophysiological studies. Later on, the Yale group by using their tryptophan cocktail replicated and extended our initial findings about the significant role of serotonin in depression. The role of serotonin in the therapeutic response has become clear, but to what extent the role of serotonin was primal in the etiology of depression was not clarified. But the findings in our studies were of importance in the development of an understanding about the significant role of serotonin in depression, because at the time, as I'm sure you will remember, there was the catecholamine hypothesis that simply put, norepinephrine up in mania and norepinephrine down in depression. Our findings did not entirely support that conclusion.

TB: Your findings were more in keeping with theories of depression advanced in Europe.

SG: Well, actually

TB: So, these were the activities in the famous Sam Gershon unit at NYU?

SG: Right. The psychopharmacology group was not only a vehicle for research. It was also a production line for very talented people to become successful.

TB: And all of them seem to remember their experience working with you, very happily. They talk about the years when these activities took place as The Golden Age.

SG: Well, it was a very pleasant time. Everybody could interact with everybody in a free environment.

TB: Is there anything else you would like to add about your research at NYU?

SG: These were the essential things. In essence, there was a psychopharmacology research group at NYU, it did have these categories of activity, and it produced a lot of very smart people.

TB: Then you moved.

SG: Yes, I moved to Detroit, to Wayne University.

TB: Could you say something about your activities in Detroit?

SG: Well, I went there as a bureaucrat, as the chairman of the Department of Psychiatry. They had that remarkable facility, the Lafayette Psychiatric Research Clinic there, and that gave me an opportunity to bring in a group of people that could be actively involved. We had a pre-clinical and a clinical geriatric program at Wayne. Nunzio Pomara came with me from NYU, and also Mike Stanley, to become head of the pharmacology laboratories. We recruited about a dozen Ph.D.'s to run laboratory programs. We had very generous support for visiting research fellows from overseas. One of them was Bernard Lerer, who came for two years, and in the first year, he got the second prize of the Bennett Award for biological research, and in the second year, he got the first prize of the Bennett Award for his research.

TB: What did he do?

SG: He was doing work on a series of things with Mike Stanley and he was also involved with bipolar disease and carbamazepine. He did studies on cholinergic mechanisms and ECT. He was involved in a wide range of activities, but each of the prizes, of course, was for a focused and directed research project.

TB: Is there anything else you would like to add about your activities at Wayne?

SG: Nothing else, except the fact that it again provided an opportunity for the development of research activities in the well-supported atmosphere of a state funded clinical research program. As you know, the Lafayette Clinic is no longer in existence. It suffered the fate of many state funded research programs throughout the whole US. The one in St. Louis, The Missouri Institute of Psychiatry, was essentially closed down. Lafayette Clinic was closed down and that's another separate problem.

TB: Where did you go from Wayne?

SG: I went to Pittsburgh to join the master organizer of the age, Tom Detre, as the associate vice chancellor for research for health sciences. And with Tom as support, we then carried out his vision of growth in the medical research programs at the University. I had the opportunity to put in place some new directions.

TB: Like what?

SG: It's important to stress that without Tom's involvement, nothing would have been possible. He saw the value of having a clinical pharmacology program. Clinical pharmacology in the US was not a major activity. It certainly had its strongest activity in the United Kingdom. It had activities in Europe but was mainly active in the United Kingdom. With Tom's assistance, we got support to develop a clinical pharmacology program at Pittsburgh. We recruited a director, an Englishman, Bob Branch, who came and developed an important clinical pharmacology program. He became director of the CRC (clinical research center) for the medical school. And again, with the support and vision of Tom Detre, we could create an imaging center, which as you know, is a very expensive toy. But it was created and there is now a positron emission tomography (PET) Center in the medical center; and a nuclear magnetic resonance imaging (NMR) Center and an NMR Spectroscopy Center that are located on two separate floors in the medical school. It is important to recognize the fact that it was put in place at a time when, in many places, the importance of such a center was debated. The importance of an imaging center is highlighted by the fact that, at this meeting, there was a major session dedicated to imaging research.

TB: What are you doing now?

SG: Now, I'm an elderly gentleman and removed from most administrative activities. I'm a professor of psychiatry. I have continued, up to recently, to be the director of an adolescent alcohol research center, which is funded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA), that I will hand over to a younger and more creative gentleman.

TB: But at this point in time, you are still the director of that center?

SG: Well, it's in transition right now.

TB: You have been very active since the 1950s.

SG: Early fifties.

TB: During the years, you have published widely. Do you remember what your first publication was?

SG: My first publication was on the embryological effect of lithium. Then I published on morphine antagonists, on succinic acid, a morphine antagonist.

TB: Didn't you collaborate while still in Australia with Barney Carroll?

SG: Right, Barney Carroll joined me to do a science degree in pharmacology in the middle of his medical training. We looked at succinic acid in carbon dioxide poisoning and found that it has

beneficial effects. Barney did his thesis on that. Dr. Carroll came to the United States, subsequently, and became chairman of psychiatry at Duke.

TB: Didn't you work in the same period also with barbiturates?

SG: That's right. We looked, in addition to antagonists to morphine, at pharmacological antagonists to barbiturates. At that time, barbiturate poisoning and barbiturate suicide were a big deal. It isn't now, but it was then, and it was important to develop analeptic treatments for barbiturate poisoning. And, we did, in fact, develop Bemegride (3-ethyl-3-methyl-glutaramide), a suitable agent for the treatment of barbiturate poisoning. It was also marketed as a mixture with barbiturate pills. It is not specific against barbiturates; it has analeptic properties, but it has not been studied beyond barbiturates.

TB: How many papers have you published approximately?

SG: I'd say about six hundred and fifty.

TB: What was the last one?

SG: The most recent ones were dealing with inositol. Lithium is an inhibitor of inositol phosphatase and affects inositol metabolism. A series of experiments were done at Pittsburgh in this area of research with a research fellow, Dr. Levine, who came to us from Israel. We found in our clinical research that inositol has an effect on treatment resistant depression, but the sample size of our study was too small to produce more than a trend.

TB: So, this was your last publication?

SG: Well, don't say the last. That's a horrible thing to say; most recent.

TB: Most recent, I'm sorry. Is there anything we left out that you would like to add?

SG: No, other than the fact that my experiences in the U.S. all produced opportunities for growth. And the people I met in the U.S., from Jonathan Cole on, all promoted growth, and the Psychopharmacology Service Center was the engine of growth in psychopharmacology in the US. I'm sure you're the beneficiary of some of that fallout in Canada. And, it should be clear that individuals can make an important difference, and that goes right down to the sort of ability to mentor other investigators and do it on a personal level. It isn't the institution or the money, alone, that creates these things. It's a matter of individuals all along the way making contributions far beyond what an institution alone can do.

TB: What would you say was your most important contribution?

SG: Oh, we listed some of the actual scientific activities, which all have a different value, but the most rewarding, really, was to work with young talented people and have a mutual interchange of excitement and growth. That really was the most rewarding, following all of these experiences.

TB: Thank you very much for sharing all this information with us.

SG: Very well, terrific.

TB: And I hope you will continue with your work, training people and doing research, even if retired from your administrative activities.

SG: Yes, I will continue with a sort of research.

TB: I hope you will continue for many years to come.

SG: Thank you very much.

TB: Thank you.

23. ALEXANDER H. GLASSMAN

TB: This will be an interview with Dr. Alexander Glassman²⁵ for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College. It is December 10, 2003. I am Thomas Ban. Could you tell us where and when you were born, about your education, and how you got involved in psychopharmacology?

AG: I was born and went to school in Chicago and spent my early life in the Midwest. I went to undergraduate and medical school at the University of Illinois, intending to go into orthopedics. I had an uncle who was quite successful, a high water mark for the family, and very anxious that I join him. I never liked orthopedics, decided I cared more for psychiatry, and wanted to be a psychoanalyst.

TB: When did you graduate from medical school?

AG: I graduated from medical school and was married, in 1958. My wife had been attending Northwestern and was from the east coast. She wanted to return for one year to the east coast before we came back to Chicago. I interned at DC General Hospital, in Washington because to practice in the Midwest, you needed a rotating internship that included both surgery and medicine. I went back to see my uncle and told him that I wasn't going to join him. He was quite distressed because he wanted to continue the family name in orthopedic surgery. It was unusual at that time for a Jewish person to be a surgeon and he was among the first orthopedic surgeons to practice sports medicine. He was a friend of George Halas, who owned the Chicago football team, and persuaded him to have an orthopedic surgeon as team doctor. Still, when I told him that I had decided not to go into orthopedics, he was terrific. He put his arm around me, and said, "Sandy, I always wanted to be a psychiatrist." So that began my career in psychiatry. I was a resident at Jacobi Hospital in the Bronx and on the faculty of the Albert Einstein Medical School. I had a public health fellowship and it gave me a lot of latitude. It was really intended to increase the number of psychiatric teachers but in the fine print it said research was a good idea. So, I thought it would probably be advantageous if I did research and applied for a grant, particularly, since I

²⁵ Alexander H. Glassman was born in Chicago, Illinois in 1934. He went to medical school at the University of Illinois and completed his internship at District of Columbia General Hospital, in Washington, DC. He completed his psychiatry training and was a faculty member at Albert Einstein Medical School in New York City. After time in the military he was recruited as a member of the faculty of Columbia University where he has stayed throughout his career. He was interviewed in San Juan, Puerto Rico on December 10, 2003.

believed the attending I worked under was unpopular with the Chair of the Department, and my position might be in jeopardy. I didn't think about research in biological psychiatry until I became interested in something that Alec Coppen was doing in England with serotonin. It was very popular to study norepinephrine in the U.S., but instead, I did a precursor study giving tryptophan to people on MAO inhibitors to see whether it altered response to the drug. I got a grant for a project that wouldn't be funded today because I had no credentials. My intention was to finish the project and go into analytic training. However, I couldn't support my family, I had two children, and go into analytic training. I had almost finished the project when the Vietnam War intensified and I was drafted. I spent two years in San Francisco at Letterman General, where I got increasingly involved in teaching about drugs and wrote a monograph for the army.

TB: How did you get involved in teaching?

AG: The reason was totally accidental and began before I was drafted. Jerry Jaffe, who did all the teaching about drugs, left Einstein to go to the University of Chicago, when Danny Friedman became Chairman there. That left Einstein without anybody to teach about drugs. There was a meeting held by NIMH to foster psychopharmacology education, and Milt Rosenbaum, the Chairman at Einstein, asked me to go. It was held at the University of North Carolina and I went, but I really felt insulted. I believed he picked me because he thought I was the least likely to succeed as an analyst, in what was a very analytically oriented department. I already had some research funding for what he considered biological psychiatry, and he thought I would like this. I met a number of people there: Fred Goodwin, John Davis, and Biff Bunny, learned something about these new drugs, went back to Einstein, and began to teach psychopharmacology, but it was still my intent to go into analytic training. When I was drafted, and the Army heard that I had been teaching psychopharmacology for several years, they were very eager for me to do so, at either Walter Reed or Letterman. I had already been to Washington for internship, so I chose Letterman. The Army was quite good to me. I was director of residency training for the first year and was having trouble financially. I was almost 34 years old and the Army salary was, I think, \$5,000. We were worried because we had one child in school and another one starting. So we put all the money we had saved into renting a house in a good school district, and then ate canned spaghetti. I got a second job consulting on patients who were problems for the California Mental Health System. I didn't know that much about schizophrenia, but I learned a lot by trying to teach it and

developed more and more expertise about drugs. I also published the tryptophan study while I was in the military. The Army gave you a half day off every week and I worked with Bill Dement in his sleep lab, at Stanford. He probably doesn't even remember, but I went down there for about a year. By the time I got out, I knew a lot about drugs and had much more of an interest in research. I also felt if I went into analytic training, my children would graduate before I would. So, because of that Vietnam War enforced delay, I thought I would try my hand at research. I talked to the people at Einstein and at Columbia. The tryptophan grant I had started was finished by Stan Plattman, who worked for Ron Fieve at Columbia with lithium. No one at Einstein had any experience with lithium, so I spent some time with Stan to learn about it. I corresponded with him, while I was in the Army, and when I left the Army, Ron Fieve offered me a job at Columbia.

TB: When was that?

AG: In 1969, I came back to New York, at Columbia, and I've been there ever since. It's now 34 years ago. At first, I worked with Ron Fieve, but that didn't work out, and I seriously thought about going back to Einstein. Then Kolb, who was Chair at Columbia, said that he needed someone to run the biological psychiatry program. Sid Malitz, one of the very early members of the ACNP, was the chief of Biological Psychiatry, but didn't have time to run the department any more. It was located on an inpatient unit that studied depression, and I took over as acting Director. There was a young physical chemist named Jim Perel, who was very gifted, and who developed a method for measuring imipramine. Until that time, we did not have methods for measuring any psychotropic drugs, including the antidepressants. You could laugh when you think about how we had to do it. It was a fluorescent method that needed a dark room. Jim's interest had been in studying the effects of methylphenidate on imipramine levels. I thought that the more interesting issue was not drug-drug interactions, but the question of whether blood levels make a difference in clinical outcome. The tricyclic antidepressants were very lipid soluble compounds, with large differences in blood levels from one individual to another, but we didn't know if it made any difference. We got a grant, in the early 1970s, to look at this issue, and with Jim, did the first blood level study in the United States. There was a group in Sweden, Folke Sjoquist and Maria Asberg, that opted to study nortriptyline because it had no metabolite and seemed easier to study. We realized imipramine was a problem because we needed to measure both imipramine and desmethylimipramine, and that was not easy, but it was the more widely used drug. Actually, the

most widely used antidepressant at the time was amitriptyline, but we couldn't get it to fluoresce, and it was seven or eight years before anybody developed a stable method to measure it. So we did the imipramine blood level study, and the results were really quite striking. There was a very real relationship between blood levels and therapeutic effects with the tricyclic drugs. Originally, our interest was entirely in people who were rapid metabolizers, who burned the drug up, had low levels, and didn't get better. Gradually, it dawned on me that there were people at the other extreme, who were poor metabolizers, had high levels, and I became interested whether being a poor metabolizer had any consequence. We had a patient who developed heart block and we published that paper in, I believe, 1977. It was interesting because that was a cardiovascular side effect that was directly related to the rate of metabolism. The patient was taking ordinary doses of imipramine but had very high blood levels. As the blood level dropped, the heart block went away. That was the first case of a tricyclic-induced cardiac adverse effect, at usual oral doses. It's something you usually see only in overdose. Those kinds of reactions, in truth, turned out to be rare, but it got us interested in the cardiac effects. We looked first at the cardiac effects in normal people, and they were very modest. The drug would prolong the QT interval on the EKG, but not in a way that produced serious problems. There were issues with orthostatic hypotension and I wanted to follow that up in a second grant, but one of the site reviewers, a cardiologist from Yale said, you shouldn't keep studying people who are healthy. We know that's safe. The question is how much danger is this in people who have heart disease? That comment got me involved in heart disease and so we did the first trial of an antidepressant in patients with overt heart disease.

TB: What about blood levels and therapeutic response?

AG: The other thing that happened in the blood level study was that patients that were delusional were doing very poorly. Also, in 1977, we published a paper before we had any blood level data, saying that delusional patients don't do as well as non-delusional patients. Nondelusional patients got better about 60 to 70% of the time. In the old days, the tricyclic drugs were very effective in inpatient populations, but they had side effects that killed people in overdose. With a good blood level, we were getting 75 to 80% of the patients that were in hospital better. But the delusional cases did very poorly. I published the paper in the *American Journal of Psychiatry*, presented it at the national American Psychiatric Association (APA) meeting, and thought everybody would believe me and accept it. I was just naïve; I didn't know for a long time that you have to advertise

your findings. And one paper doesn't do it. You have to write half a dozen. We wrote a few papers about delusional depression and over the years it has come to be accepted. Nowadays, you are taught to use combined treatments, but it took a decade before that was accepted. That began as a clinical observation in a group of people in a blood level study. A lot of our time in the 1980s was spent with cardiovascular studies because the tricyclic compounds were problematic drugs in people with overt heart disease and in overdose. I thought, by the mid 1980s, I had exhausted the area because we knew everything there was to know. I became interested in stimulants because some patient told me that his amphetamine was much better than my imipramine and that he didn't want to have anything to do with tricycle antidepressants. I began to study amphetamine in people with major depression to see whether they were useful or would augment antidepressants. As soon as I got seriously involved, it occurred to me that the stimulant that depressed people used most often was nicotine.

TB: So that is how you got involved in smoking.

AG: That got us into a whole series of studies with smoking. We got the idea that maybe clonidine would suppress nicotine withdrawal symptoms. We did a study which was published in *Science* in the late 1980s and showed that clonidine had an effect on nicotine withdrawal. That seemed like a sidetrack. I wasn't sure I wanted to pursue it, because my experience for 15 years, had been working with depression, and I didn't know much about smoking. But we published it because it was a novel observation. No one had ever shown a non-nicotine drug could affect withdrawal from nicotine. The truth of the matter is we got a patent on it, which never turned out to be very valuable. It took a lot of time. We did a study with normal subjects because it seemed hard enough to stop smoking without being schizophrenic or depressed. Being a psychiatrist, it was easy for me to do a psychiatric interview, so everybody at the smoking clinic had a standardized psychiatric exam before they entered the study. We made a startling observation; an astounding number of smokers had a history of depression. Once we saw that, we looked to see whether it affected their quitting smoking, and people with a history of depression were much more likely to fail. It was a small study. I think there were 88 patients. Clonidine turned out to be a very mediocre smoking cessation drug. It worked, but it wasn't as effective as the nicotine patches or gum. But I got interested in the relationship between depression and smoking and thought that maybe an antidepressant drug would be useful in smoking cessation. We suggested that at an APA meeting.

We did some pilot studies, and looked at a number of antidepressants, including bupropion. Linda Ferry, in California, saw our paper in the *Journal of the American Medical Association* linking depression with smoking cessation failure, and did a double-blind trial at the Veteran's Administration hospital. She had, I think, 42 smokers, half on placebo and half on bupropion. There was an impressive quit rate on bupropion. The drug manufacturer, Burroughs-Wellcome, pooh-poohed the idea; so, she called us and asked how we measured depression. We gave her scales and taught her how to use them. Her mother, recently retired from the California school-system, administered them. Linda studied 192 smokers, all free of depression, and bupropion still worked. That led to Zyban, bupropion in a new formulation for smoking. There were headlines about depression and smoking, and I was invited to give presentations to non-psychiatric audiences.

TB: By now you must have been pretty pleased with your findings.

AG: Yes, but there was also a part of me that was concerned or unhappy. I don't know exactly how to put it. I had always had in my mind not just the cardiovascular effects of antidepressant drugs, but the cardiac effects of depression itself. I had a strong bias that depression was causing heart disease. The literature was controversial about whether increased mortality was from depression, or just the drugs used to treat it. There was clearly an increase in cardiovascular mortality in depressed people, but all the patients came from clinics or hospitals, and were all medicated. So you couldn't disentangle the medication from the diagnosis. Jane Murphy did a community epidemiological study, in 1988. I honestly thought that once she went into the community, the relation between depression and death would disappear, because the cases would be much milder. I thought you'd need a really severe major depression to produce heart disease.

That's not what happened. She showed a relationship, and a couple of years later, the Yale group replicated that. In the late 1980s, when we started on our smoking work, I thought the depression and heart disease relationship was nailed. But I began to realize it could simply be that depressed people are more likely to smoke, and smoking causes heart disease, and no one had ever controlled for that. At a meeting of the American Medical Association (AMA), in Chicago, I met a cardiovascular epidemiologist by the name of Anda. He had replicated our observation about smoking and depression, and its ability to interfere with cessation. When I asked about his data set, Anda had one that prospectively recorded deaths. He not only knew whether someone was a

smoker and if they'd quit, he also knew if they died. We could look at the relationship between depression and death, controlling for smoking. He convinced me you have to control for all the cardiovascular risk factors, not just smoking. We published a paper, in 1993, showing that even controlling for all cardiovascular risk factors, the relationship between depression and cardiac death persisted. That got me more and more into this issue of depression itself affecting heart disease. When I had gone into smoking, I thought it was unrelated to depression. It turned out to be very much related; so much for planned research.

TB: You got also involved in mortality studies with depression. How did this happen?

AG: In the early 1990s, a Canadian, Nancy Frazier Smith, did a psychiatric exam on 222 post MI patients in cardiac intensive care and followed them for six months. People with major depression were almost four times more likely to die. Even controlling for risk factors and severity, this has been a very consistent finding. But hers' was really the landmark study. Even though there were a very limited number of patients, I felt we needed to do a clinical trial to see if treating depression would reduce mortality, and that was really the beginning of the sertraline antidepressant heart attack randomized trial (SADHART). That study had a very rough beginning, nobody wanted to do it. Wilma Harrison attended the ACNP for a number of years as a representative of Pfizer. She eventually ran the CNS division and she was somebody special. Most of the company people did not want to do the study, but Wilma insisted it was crucial. After about two years of in-fighting, they eventually agreed to do a pilot study. But we demonstrated that we could collect the patients and do the measurements and we had some pilot safety data, so they didn't have to worry that anything terrible would happen. The definitive study did not start until 1997 and wasn't published until 2002. The results were beyond our wildest dreams. I thought I was doing the world's largest pilot study. It was really a stepping stone. I wanted to do a mortality study, but because there was no safety data, and we needed that first, the design did not have the power to show if treating depression reduced mortality. That would need 3,000 to 4,000 patients, if there was a 20% reduction in mortality, and I didn't think it would reduce it by that much. A 10% reduction would still save 1,000 lives a year. But there is another aspect, in addition. It would change the stigma attached to depression, both in the patients themselves, and in physicians. Many physicians still don't accept that depression is an important condition. If you could show that treating that condition would reduce mortality, then they would pay attention to it. So I'm still working to get

that definitive trial. The SADHART results suggested that there was at least a 23% reduction in life-threatening events. It just missed being a trend. But the study and sample size was nowhere near adequate to look at mortality. It did prove safety, and that makes a larger study much more doable. And then, the NHLBI study, encouraging recovery in coronary heart disease (ENRICH), showed that psychological treatment reduced depression, but it didn't change mortality. The ethics committees said, if you had a patient with a Hamilton Depression score of more than 24, you have to give them an antidepressant. It turned out that about 20% of patients, for one reason or another, were already on an antidepressant drug, usually an SSRI. But in ENRICH, drug use was not randomized, nor was it controlled. Some people started it early, some started it late. Nevertheless, there was a 42% reduction in mortality in the drug group, compared to the non-drug group. You would expect a higher death rate in the more severely depressed, but there was a 42% reduction in mortality. So it looks very much as if antidepressants reduce mortality. There are things to be done, but so far that's the story.

TB: There are things to be done you said. What should be done?

AG: What would I like? The most important thing is to do a simple definitive trial; to take 4,000 patients and randomize them to an SSRI or placebo. I'm a consultant for the American Heart Association, on their standards of care committee, and they look at our data and say, it's very suggestive, but it's not definitive. It can't be made a standard of care on the evidence we presently have. If it isn't a standard of care, some people will do it, some people won't. The drug companies can't really advertise it because there is no evidence that the FDA would accept. If we did a definitive trial, and showed a reduction in death, that would have such an impact on how other physicians look at depression and how the patients looked at themselves. I honestly think that depression is a disease of the whole body. The same story exists with stroke. There is not as much evidence, but it looks very much like it. And there's very good evidence that bone metabolism is affected by depression. Once you prove that treating depression reduces mortality, then there will be a whole slew of studies looking at why. As a group that studies psychopharmacology, we put up fences between other disciplines that limit our understanding. We may have one of the best cardiac drugs. This may be beneficial in anyone with bad heart disease, not just in depressed people. If we reduce death in depressed people with an SSRI, people will look and see if it works in all cardiac patients.

TB: Is there anything else you would like to talk about or add?

AG: No, I don't want to add anything. That's fine.

TB: Well, then, I think we should conclude this interview with Dr. Alexander Glassman. Thank you very much.

AG: It's a pleasure.

24. BURTON J. GOLDSTEIN

TB: This will be an interview with Dr. Burton Goldstein²⁶ for the Archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the College, in Hawaii. It is December 13, 2001. I am Thomas Ban. So, Burt, let us start from the beginning. Where were you born? Tell us something about your education and so on.

BG: First, let me say what a pleasure and honor it is to be here this afternoon to be part of this wonderful organization that has meant so much to me. I often get asked which organization I consider to be my most important, when people come into my office, and I say, "It's the one from which I don't have a diploma, the American College of Neuropsychopharmacology." I was born in Baltimore, Maryland. I was educated in the public school system in Baltimore, elementary school, junior high school, and high school. And then, upon graduation, which was in 1949, from high school, I entered college at the University of Maryland, School of Pharmacy. I had never thought about being a physician. I was interested in pharmacy. But during my four years working for my bachelor's degree in Pharmacy, I became interested in pharmacology, and probably, the pharmacology and some of the chemistry were the courses I did best in. And then, upon graduation, it was during the Korean War, I was drafted, and found myself in infantry basic training. It was quite a challenge. I learned that I had, perhaps, talents that I had never really thought I had before. Then, they sent me to advanced infantry basic training and that was an adventure, but interesting. I never thought that I could do some of the silly things that we did in the military, like painting white stones black and black stones white, but it was interesting because I got pushed to my limit and I learned what I could do. And then, my time was up and I had to figure out what was I going to do with my life now, and I thought, well, maybe what I'll do is go to medical school. Now, that was a rather ambitious undertaking, because I did well in pharmacy school, but I certainly wasn't outstanding in terms of my grades. I applied only to the University of Maryland and figured, if I can't get into my home state university, I'm not going to get into any

²⁶ Burton J. Goldstein was born in Baltimore, Maryland in 1930. He trained in Pharmacy at the University of Maryland. After military service in the Korean War, he completed his M.D. at University of Maryland and his residency in Psychiatry at the University of Miami where he stayed on faculty. He was interviewed at Waikoloa, Hawaii on December 13, 2001.

other university. And I got accepted on the provision that I take a year or two of sort of liberal arts courses.

TB: What year was that?

BG: That was in 1956, I believe. I entered medical school, I think, in 1956 and graduated in 1960.

TB: So, you did not pursue a career as a pharmacist?

BG: No, I never did. The pharmacy helped me, financially, to get through school. There was the GI Bill and I was getting, I think, a hundred and eighty dollars a month, but I had to pay tuition out of that and everything else. As a pharmacist, I could work in the summers in the pharmacy and I made all of two dollars an hour, but I worked sixty or seventy hours a week and made a hundred and twenty or a hundred and thirty dollars a week. In 1956, that was a lot of money. So, I was able to pay for my medical school. My GI Bill ran out, as I recall, at the end of my junior year but I got a scholarship for my last year of medical school. I graduated in 1960, and then, like most of us, was trying to decide what path I should go. My role models were some of the people in the department of psychiatry; and so, I said, I want to go into psychiatry, and decided that I would go down to Miami to do my internship there. I applied to Jackson Memorial Hospital, a large community hospital of the University of Miami, for residency. So, I did and I was accepted. I had a NIMH Fellowship during my residency years, so I took off, I think, in more of a research venue. But our program didn't really encourage me to do research, because our hospital was a county hospital. At that time, south Florida, particularly Miami, was undergoing a lot of turmoil and transition because of Cuba. Castro had just come in the late fifties and early sixties. I was there in 1960 and '61, as an intern, and from 1961 through '64, as a resident. At that time, there were a tremendous number of extremely well qualified Cubans there, who left Cuba, because of the persecution there. And, that went on for several years and the population of Dade County that was served by the hospital, was literally exploding. What I am saying, is that our clinical work overshadowed almost anything else. Everybody was so involved in patient care that research was put on the back burner. But, I pursued and I was able to get involved during my second and third years with folks that were doing other types of psychological research. I don't even remember what they were doing but I learned from them some research strategies, research methodology that helped me quite a bit. And then, by 1964, I finished my training and our Professor and Chairman, John Caldwell said, "You know, if you're interested in research, why don't you stay on?" I was

really flattered and honored. So, I was able to join the faculty and I remember him telling me, “Well, I’m now going to be able to pay you ten thousand dollars a year. That will be your salary; and for seeing patients, you’ll get another ten thousand dollars.” Well, I had never heard of that much money in my life, so, I thought I was going to be a very, very wealthy person, and not just having an opportunity to become involved in research. Then, I don’t know how it happened, but I met some of the people up at the Psychopharmacology Service Center, which included you and your dear friend and colleague, Heinz Lehmann, Jon Cole and George Crane, who you may remember. By that time we had already done a couple of studies with haloperidol and when I started talking to George, he said, “You know, not too many people in the country have much experience with haloperidol, would you like to get involved in a study?” And gosh, that was flattering, because I didn’t know very much about federal grants or anything of that sort, and then, George, as obsessive he was, and he really was obsessive, put a protocol together. It was a wonderful, wonderful learning experience. It was duplication, on a small scale, of the nine hospital collaborative study, the pivotal study in determining that neuroleptic drugs were effective in the treatment of schizophrenia that was completed, in 1962.

TB: So, after completing your residency you stayed on the faculty of the Department of Psychiatry at the University of Miami. Didn’t you have something published while still a resident?

BG: Right. Well, I began publishing while I was still a resident. I remember our first paper was on Cogentin (benztropine mesylate). It addressed the question, whether it should be used before EPS developed or wait until the first signs appear. It was a terrible paper and it was rejected by a couple of journals before, finally, it got accepted.

TB: So, your interest was in clinical pharmacology?

BG: It was something that caught my interest, even though I didn’t know any people in the field, and I was very fortunate to be able to have opportunities to pursue it.

TB: How did you get involved with the Cogentin study?

BG: Well, I think that came from watching patients develop EPS, who were on Trilafon (perphenazine) and Stelazine (trifluoperazine). They were taking high doses and they developed extrapyramidal side effects. I began to read about Cogentin and we would, obviously, use Cogentin in the treatment of EPS. But, you know, Tom, what I think really triggered it, now that you ask me the question, was that when I was an intern there was a man, who came into the

emergency room and his jaws were locked, like this. Everybody said, this man has tetanus, but when I asked him to write out what medications he had been taking, it turned out that he had been on, either Trilafon or Stelazine. So, what we saw was an extrapyramidal side effect; he was having a dystonic reaction. There are very few times in my life I've been a hero, but I can tell you the people in the emergency room thought I was really smart, because I was able to figure that out, and especially when I gave the man, I think one or two milligrams Cogentin IV, and he would get to talk again. Gosh, I could walk on water that day. They really thought I was smart.

So, I think that may have been behind the Cogentin study we did.

TB: Could you say something about the study?

BG: We set up a small study but I don't remember the results clearly but I think it was that you could not predict who was going to get EPS. So, it probably isn't worthwhile to give Cogentin prophylactically. But, I learned from that study a little bit more research methodology to work with patients in a double-blinded fashion, and in general, I learned about patients and research. And, that was, I think, the beginning.

TB: Did you do any other studies while a resident?

BG: No, I think, at that time, I was working with a psychologist, who was doing some work in some abstract field, and that, I guess, was the only pharmacological work that I did, as a resident. The University of Miami was, at the time, only about ten years old, and the Department of Psychiatry had, perhaps, only four full time psychiatrists. So, it was a very young department trying to take care of enormous numbers of indigent patients; the clinical load overshadowed everything else. So, that takes us up to about 1964, to the time of meeting George Crane, who helped us to design the haloperidol study. I was fortunate that along the way I met Dean Clyde, who had come to Miami, I guess a couple of years before, to set up the biometric lab at the University. Now, the teaching hospital is in the center of the city and the University, itself, is on, what's known as the Coral Gables campus, some sixteen miles from the medical center, and that's where Dean's shop was set up. And, as you know, Dean was sort of a unique kind of individual. He was, in many ways, a loner, but Dean and I had a kind of rapport that was very, very wonderful. I never saw Dean get particularly close to people. But we had a close, and not just professional relationship. What impressed me about Dean was not only his dedication but also his abilities. He set up this biometric lab on the fourth floor of a brand new building that was half of the size of

a big Costco warehouse and this whole floor was all of Dean Clyde's computers. That was just overwhelming and I got to work with him. I was working with Dean when he was doing some work with the Cuban refugees. When the Cuban refugees were coming into Miami, they would come over to what was known as Freedom Tower, and down there, they had all kinds of social service support, and Dean was asked by either the State Department or someone to administer the Clyde Mood Scale to these people. One of the humorous events about that was, when Dean Clyde said to us, "You know, all these Cubans are coming and the scale is in English. We need to translate it." So, I got one of my faculty members, who had just come over from Cuba, to translate the scale. He was a very erudite physician, trained in Boston. He knew English and he knew Spanish and he translated the Clyde Mood Scale into Spanish, but none of the people coming over could understand his upper class Spanish. And then, I found a person that was of lower social status but no one could understand him either. Finally, we were able to find a social worker who did it. We worked together hand in hand, and then, when we started our haloperidol work with George Crane, Dean was part of setting up the design. I wish I had some of the slides from that study. It would be fun to look back now, thirty-five years later. We could keep patients in the hospital for three months. Today, you keep people in the hospital for four days and people are after you about it. But, we had a design, in which patients were treated with Haldol (haloperidol) or Trilafon (perphenazine), in a blinded fashion, for eight weeks. At the end of eight weeks, we'd have a clinical conference and if they were considerably improved, we would watch them for another eight weeks. And, if they relapsed, they would be started on the drug they improved on. But, at the end of eight weeks, if they didn't improve, they were crossed over to the other drug and treated for another eight or sixteen weeks. At the end of the study, what we found was, basically, that haloperidol was an effective neuroleptic drug, which sounds foolish today, just as though the nine hospital study sounds foolish today, because everybody now just assumes that we always knew that those drugs were very effective. I think the most interesting part of that study was that at the end, we could firmly say that the dose of haloperidol should be fifteen to twenty milligrams a day. I remember, once, that Dick Shader from Boston called me and asked, "Burt, what is the dose of haloperidol?" And I said, "Dick, it's sixteen to twenty mg. a day, you don't have to go up to those megadoses." What actually happened was sort of an industry push. They talked about rapid tranquilization, as you remember, but rapid tranquilization really translated for them to rapid

haldolization. So, a lot of Haldol was sold; people didn't need ninety milligrams of Haldol, twenty mgs was just as good.

TB: Today, you could go even lower.

BG: Sure. I remember that we were particularly honored because the introduction of haloperidol, once it was approved by the FDA, took place in Miami. We had a symposium and Paul Janssen was there. At the same time, we were starting several industry sponsored clinical studies. And then, I wrote with Dean Clyde the chapter on the butyrophenones in ACNP's Psychopharmacology, A review of Progress from 1957 to 1967. We put John Caldwell's name in it, as a third author, because he was always a really tremendous support.

TB: So you did your research with haloperidol in collaboration with Dean Clyde?

BG: Yes, with Dean Clyde. I think Dean was probably the person who got that study for us, because I was unknown, and Dean was a known entity; he certainly deserves the credit.

TB: It seems that study was very important in your career.

BG: Well, I was so fortunate at that time because I began to meet a lot of people. I met Nina Schooler, Jonathan Cole, and Arnie Friedhoff. The two people I worked closest with were Leo Hollister and Bert Schiele. They were not only professional friends but very, very close friends. Yesterday, at the memorial services, my eyes welled up. I just thought about Leo and what a tremendous human being, wonderful man that he was. I knew him so well. Much of what Ken Davis spoke about, he could say, in terms of having worked with him as a resident, but I knew him in such a personal way and his son, Matt, who was somewhat autistic and schizophrenic, and how Leo took care of that child. You know, that kid would have never survived if it was not for Leo's nurturing. And that was another side of him. I've been so blessed to be able to work with so many wonderful people.

TB: Let's get back to chronology. Are we now in the late 1960s?

BG: We are into 1967 now, and we were watching a lot of Karl Rickels' work, at the time, because our hospital was somewhat similar to Karl's hospital, the Pennsylvania Hospital, that had a large indigent population. And, we became aware, as did Karl Rickels, that there were influences to response and side effects that went beyond, and were outside of, the pharmacology of drugs. As an example, if you had a lower socioeconomic group of people that were, perhaps, on welfare, they didn't object to sedative effects, which we would call side effects of a drug, as much as a

middle class person, who had to get up the next day and go to work. To overcome this problem, Karl Rickles was very fortunate to be able to get primary care physicians as part of his network. So, he had indigent patients and private practice patients, and so, he could study the same drugs across these groups to have a better sense of what the efficacy and side effects of these drugs would be. We tried hard to replicate what Karl did, but we couldn't do it, and ultimately, came up with the idea to recruit symptomatic volunteers that would be a population similar in socioeconomic factors as private patients? And, we worked for a while with Leo Hollister and John Overall in studies, taking three populations, one, an indigent population, second, a private practice population, and third, a symptomatic population we get through public notice. So, we applied for a grant.

TB: When was that?

BG: We are in 1968 now, and we had a grant to study the symptomatic volunteers and where they fell into the spectrum. And, as it turned out, our hypothesis was accurate that these folks were socioeconomically similar to the private practice patient. I guess I was probably the first using symptomatic volunteers. And today, I asked Paul Leber of the FDA, "Paul, how can I find out how many drug trials have been done since 1970, using recruited subjects?" And, he said, "I have no idea; you'd have to ask the drug companies." Obviously, they don't have any idea, either, but I would imagine that, just not in our field of psychiatry, but also in other medical disciplines, you can find many studies done on symptomatic volunteers recruited by advertising in newspapers or TV. I, personally, am most proud of this because I think the use of symptomatic volunteers facilitated clinical drug development across the world. I doubt that there would be enough patients for any type of disorder without the use of symptomatic volunteers for the drug development we have. So, I feel very good about that.

TB: So, the idea of working with symptomatic volunteers comes from you?

BG: I published on it first, in 1970, and I think, if I look back on my career, that's probably the greatest contribution I made, because it certainly has facilitated drug development and drug discovery.

TB: Besides the haloperidol grant and the symptomatic volunteer grant, by that time, you attended, quite regularly, the annual ECDU meetings, right? Besides the grant for the haloperidol study, you also had a grant from NIMH? Any other area of research you had been involved with?

BG: We were doing a lot of drug trials, but then, we became aware of what was that the flip side of psychopharmacology, substance abuse. And, there was a Catholic Priest in the Miami area, Monseigneur Walsh, Brian Walsh, who came to see Jim Sussex, the Chairman of our department, John Caldwell, and myself and he said, "You know, we're having problems with our methadone clinics. Would you all look into this?" And I looked into it, and also looked at some of the early literature from Freud about the use of cocaine in depression and thought one could make a pretty good case that many individuals that got hooked onto heroin or cocaine or other drugs really were trying to treat themselves for depression. And, I remember talking to Mitch Balter about this up at NIMH and some of the people over at NIDA, and we put a grant proposal that went through NIDA to study this question. The idea was that, perhaps, some of these individuals that have been hooked onto heroin are now being treated with methadone, still were not adequately treated, because nobody was treating their depression. So, we set up a Methadone Clinic, under the auspices of Monseigneur Walsh, and in that study, when someone would come into the methadone program, we would do the Hamilton Scale, and then, four or five weeks later, we would repeat it. Then, we decided to study these people by treating half the group with methadone plus an antidepressant and another group with methadone and placebo. To provide them with a supply of methadone was OK; but at that time, we only had tricyclic antidepressants, and we could not provide patients with a supply of these drugs for twenty or thirty days because if they would overdose enough they could kill themselves. We solved their dilemma by giving them doxepin, Sinequan in liquid, because it was safer if they overdosed. It was a 12 week double blind study and we found some decrease in depression scores. The greatest change that we saw was in patients' behavior. They seemed to get into less trouble with police. There was a host of improvements, mainly of the social behavioral type. Now, if you follow the literature in heroin addicts and methadone programs, there is a body of literature, which has been emerging over the years that these individuals may respond to antidepressants, plus their medication, because of their underlying depression. While we were doing this study, there was a young man that had just come down from Yale, looking for a job to get more involved in psychopharmacology. I got a career award from NIDA, and we hooked him into the methadone study I just told you about. He seemed to have a real interest in it. The young man's name is Brian Weiss, and one day I asked him, "Brian, would you be interested in an academic career?" and he said, "Yes." Then we put a grant together,

with me as PI and he as a Career Teacher Student, and we got the grant for three years. Well, in the second year of the grant, Brian came to me and said, “You know, I don’t think this is really what I want to do. I have an opportunity to go over to the Mt. Sinai Hospital where they are going to start a Department of Psychiatry.” Mt. Sinai is a private hospital in Miami Beach, a very well-funded hospital with about six hundred beds. It is very different from the Jackson Hospital, which is taking care of, primarily, indigents. And I said, “You know, if that’s what you want, I wish you the best of luck.” So, Brian goes over to Mt. Sinai and begins to see a lot of private patients. The thing I know, Brian is involved in past life therapy and writes this book, “Many Masters Many Lives,” and he became very, very famous. I think, now, there’s about a year waiting list for somebody to see him and his charge is about five hundred dollars an hour to take you back into a life that you may have had before. While it was a disappointment for us, it gave Brian Weiss stardom and recognition around the whole world, as a matter of fact.

TB: So, it seems you moved from research with psychotropic drugs to addiction research.

BG: Had I stayed more with psychopharmacology and Haldol, I probably would have more recognition in that area, today, but I’ve always seen myself as a person whose allegiance was to the medical school, first, and to me, second.

TB: I see.

BG: Then I got a call from the Department of Education, and they said that they were putting together across the United States an educational program to reduce the demand side of substance abuse in elementary and junior high school students, and they would like Miami to submit a proposal to go along with five other regions in the country. And, it’s hard to say no, when you’re asked to do something. So, we put this proposal together, along with some other people, and that was funded for about six or eight years, up into the mid-nineties, and I was the PI for this whole study that came out of Miami. I think the project did some good, but it’s always hard to measure because one political administration puts emphasis on supply and goes after the people that grow drugs and bring drugs into the country, whereas another, puts emphasis on reducing demand. And for the administrations that were looking at reducing demand, we did a good job. When the funding switched to increase the number of DEA agents, helicopters, and people that would do interdiction, we had to close shop on that. So, that really brings us up until about the mid-nineties, and during these years, I served as vice-chairman in the department.

TB: So, in addition to your research activities, you also served as Vice-Chairman of the department. For how many years were you Vice Chair?

BG: I had been Vice Chairman for ten or eleven years. Then, Jim Sussex, who was Chairman, retired in 1983 and I was asked to be Interim Chairman. And, I was a serious candidate for the job of chairman, but I think that the Dean felt that, while I had many talents, I probably was not as good an entrepreneur as somebody, who might come in from the outside. And, I must tell you, I was very disappointed for a few months. One of my friends said to me, after Carl Eisdorfer became Chairman of the department, that "You're going to be the happiest faculty person in about three months." I didn't believe him, but he was absolutely right, because I could go on teaching, doing my research, and not have to worry about having to take care of everybody's salary and do the kind of things chairmen do.

TB: When did Carl Eisdorfer become chairman?

BG: Yeah, Eisdorfer came in 1986.

TB: And you continued with your research. Now you did some research with tricyclic antidepressants, but that had to happen before.

BG: Well, yes, we studied tricyclics.

TB: You had already talked about some of your research with doxepin. Did you work with any of the other tricyclics?

BG: Oh, gosh, we worked with desipramine and protriptyline.

TB: Didn't you do also some work with nortriptyline?

BG: Nortriptyline? I can't even remember, Tom, but we've worked with.....

TB: Imipramine?

BG: We worked with imipramine and protriptyline. We worked with most of the tricyclics and we worked quite a bit with trazodone, and then, we went on to work with the SSRIs. So, I think, we've worked with a whole spectrum of the antidepressant drugs. We also worked with many of the anxiolytics that never came to market.

TB: Are you still working with antidepressants?

BG: I am, but when I get the call, I move on. In 1995, there was a football coach at the University of Miami, who had a positive drug test, and the university lost thirty-two football scholarships and also got into really big problems with the NCAA. And the next day, the president of the university calls some of us together and wanted to have a new drug policy. Of course, if your president wants

a new policy the next day, you become very creative and you adopt a policy that already exists. So, I gave him the policy from the transportation department, which calls for a medical review officer. And he liked that and gave me the job. So, for about six years, one of my jobs at the university has been to run the drug education/drug testing program for the athletic department, which has been very successful, because we test all our athletes three or four times a year and we've just seen a very few positives. It's just been a wonderful, wonderful experience.

TB: Any other project you would like to talk about?

BG: I also work in the Health Service Research Center at our University, with colleagues from different disciplines that is funded by NIDA and headed up by Clyde McCoy, who's Chairman of Epidemiology at our school. The Center concept breaks traditional departmental lines; and so, you're now able to work with colleagues of different disciplines, who may have similar interests. As you know, we have a large number of chronic drug users in the South Florida area, and one of the problems has been how these individuals get into the health care system and how the health care system reacts to these individuals. So our Center is focused on chronic drug users. In the first phase of our first project, we had done a similar study I had talked to you about, and we had each subject fill in the Zung Depression Scale. And what we found was that thirty-five to forty percent fell into the moderate to severely depressed range. So then, the question was, are these depressed folks different from the non-depressed? And, sure enough, they all are, and much like the non-drug using population, there are more female than male depressed drug users. We also found that depressed drug users are less likely to be working, more likely to have multiple somatic complaints, and their point of entry in the health care system is generally the emergency room, as opposed to a clinic or a primary care physician, which costs a lot more. Going to an emergency room is an expensive proposition and we figured out that on average, a depressed substance abuser costs the system somewhere between fifteen hundred and two thousand dollars more a year. So, now, in the second phase of this project, we are looking at these folks and we have broken them up into three groups, one gets pharmacologic treatment with antidepressant, another pharmacologic and psychosocial treatment, and the third is used as a general control group to see if treatment of depression might have a positive effect. So, that's what we're doing right now.

TB: Is this project your primary involvement these days?

BG: Yes, I'm not doing clinical trials now. As a senior citizen, I'm a mentor to those in the department who want to do clinical trials, helping them to develop their protocols and their research strategies. Recruitment of subjects is extremely difficult. So, I've been working with some members of our faculty that are looking at atypical neuroleptic drugs, and I've been working with some people who are doing some work on some of the mood stabilizers.

TB: So, when did you actually stop doing clinical trials yourself?

BG: In 1993 or 1994, for administrative reasons. Dr. Eisdorfer wanted to reduce the number of divisions in the department and wanted that people do clinical trials on their own and not as part of a division. So, that was an administrative decision and that was fine with me, because I was involved in some other projects at that time.

TB: So, after 1993, you really did not any longer do clinical trials yourself?

BG: No, I wasn't involved in clinical trials myself. .

TB: But you were involved until that time. Were you involved with clozapine?

BG: Well, my division did a lot of work with clozapine; we did a lot of work with atypical antipsychotics, but my personal interest has probably been much more with antidepressants than with anxiolytics.

TB: Didn't you do also some research with mood stabilizers?

BG: This has been mostly done by Paul Gutnik in the department.

TB: Of all of your contributions, which one, would you consider the most important?

BG: I think the work with symptomatic volunteers. I'm very, very proud of that. I think the other contributions have been more on a local basis, as for example starting psychopharmacology at the University of Miami. I think that, on a national level, my involvement has been very much to be involved with the ECDEU, the NCDEU, and with ACNP. I've been on various committees of the college over the years. I tend to be a sort of a low-key person, someone that's part of the team, rather than, necessarily, the team leader.

TB: You mentioned at the beginning, you worked with Leo Hollister and Bert Schiele. What did you do with Bert?

BG: We worked very closely together in some of the collaborative studies. But, Leo and Bert were my mentors and role models. I hadn't worked with you quite as much, individually, but I remember being up at a Montreal meeting, reporting on our work, that you and Heinz Lehmann

organized on the thioxanthenes. I did a lot of the work, as you did, with Navane, the thioxanthenes, and I remember the conference that was put together up in Montreal and published that little book on the thioxanthenes. I guess the most humorous person I've ever worked with was Nathan Kline. Nate was funny and we had a wonderful relationship. I would get calls from Nathan, every now and then, at odd hours in the morning, telling me that he was flying in the Pfizer airplane between LaGuardia and Groton, and I'd say, "Well, Nathan, why are you calling to tell me this? Is something going on?" He said, "No, I just wanted you to know where I was." There were things of that sort. I remember, once we were talking about setting up a teaching program for psychopharmacology for Haitians, because he was very much involved with the government of Haiti.

TB: He created a psychiatric research institute in Haiti.

BG: Yeah, and unfortunately, he got ill and was never able to pursue it.

TB: During the years you have published quite extensively. Would you like to elaborate on any of your papers?

BG: Recently, Paul Gutnik and I published a three part article on the SSRI's in the International Journal of Psychopharmacology, that addressed the pharmacology, the various uses, and the adverse effects observed. And, I think, that's the direction that I'm moving in more now, in terms of developing review papers and trying to look at the totality of the field, as opposed to a particular clinical trial or subject. We published on a group of chronic drug users last year in the Annals of Medical Sociology. So, I think that's where I am, right at this point in time.

TB: Are you still working in the department?

BG: Oh, I wear several hats in the department. I am involved in the supervision of residents. We're involved in managing a couple of the psychiatric benefits with some of the local HMO's, so I'm on some of the utilization review committees, which I enjoy doing; so my plate is pretty full.

TB: When did you become a member of the ACNP?

BG: I think I became a member in 1967, and a Fellow, sometime in the seventies. Then, I became a Life Fellow about five or six years ago.

TB: Which committees did you serve on?

BG: On the Finance Committee. I've been involved with the liaison committee between industry, academia, and the college. So, I try to stay active. I follow also the CINP.

TB: You were also active in the ECDEU program. Weren't you instrumental in moving the meetings to Florida?

BG: I think the problem we were having was that we couldn't get them out of Miami. Everybody was saying we want to go somewhere else, but the powers up at NIMH seemed to like Key Biscayne. So, I was certainly involved with the ECDU.

TB: Were you involved in organizing those meetings?

BG: I was very much involved in the organization of the meetings.

TB: For how many years were you involved?

BG: I think for at least for ten or twelve years. And, you know, Tom, I guess that's part of my personality. I tend to forget a lot of those things that have to do with me, myself.

TB: Would you like to mention a few people you worked with at the university?

BG: Oh, gosh, I worked with Ben Browser. Ben was my earliest colleague and he had a real affinity for psychopharmacology. But, unfortunately, he had some heart problems and had to retire about six or seven years ago. And then, Hy Denber called me one day and he said, "Burt, I have this wonderful, wonderful resident, Roberto Domingos, whose family is in Miami, and would like to come to Miami. And he was one of the best recruits I've ever had. Roberto is just a really solid citizen. Unfortunately, his career in psychopharmacology lasted about ten years, and then, Carl Eisdorfer tapped him to take care of all the administrative research issues in the department. So, he's, unfortunately, not doing research but more involved in the protection of human subjects, issues that come up in every medical school, now. Oh, and there are about another five or six people that were with us for periods of time. I think the greatest contribution, in developing these people, was that, even though, they didn't stay in psychopharmacology, they developed an appreciation, in terms of what clinical trials were about, understanding pharmacology a bit better and being able to understand medications better. And, there have been a whole slew of them. I would imagine, over the course of the years, we've had at least twenty five or thirty people. I guess there's one other area that I failed to mention; recently, the department was awarded one of two grants in the United States. It's from NIDA to develop a clinical trial network for substance abuse. And, it combines psychosocial treatments with pharmacological treatment. The weakest

part of the grant was the pharmacological until Roberto and I got involved in it. And, once we got involved in it, the project had funding. But, I think, had we not been involved, they would not have gotten funding, because they had only good psychosocial expertise, but not pharmacological. We worked hard with these folks to get their grant and will continue to work with them as consultants.

TB: You were professor of psychiatry and pharmacology at the university?

BG: And, epidemiology.

TB: So you had appointments in three departments. Were you actively participating in the activities of the Department of Pharmacology?

BG: Only peripherally, only in terms of Psychopharmacology. I'm much more active with the Epidemiology people, now, than with the Pharmacology people, because of their Health Services Research Center, which I think, is going to be a model type of program in terms of developing Centers for medical schools, where colleagues can work together without departmental lines.

TB: Have you written or edited any books?

BG: Way back in the past, I think, I was involved in editing four.

TB: You were involved in organizing several symposia?

BG: Yes, a haloperidol symposium and a thiothixene symposium; I had a lion's share of responsibility in organizing the haloperidol symposium.

TB: Are you the recipient of any honors or awards?

BG: I am listed in Who's Who in America, Who's Who in the World, and Who's Who in American Medicine. In 1994, Good Housekeeping had a listing, and I was listed among the 183 Best Mental Health Professionals in the Country and among the 22 Best Known Physicians treating depression. I was the recipient, also, of some teaching awards at the university.

TB: Is there anything else, you would like to mention?

BG: Well, I'm very proud of my family, my wife, Linda. We have six great kids, the Brady Bunch, and they're all wonderful, wonderful. They're not so much kids. They go from their thirties down to their twenties, but they're all very good kids. They've all made us proud. Unfortunately, none have gone into medicine, but we've been blessed in having a good family.

TB: So, with this, we should conclude this interview with Dr. Burt Goldstein. Thank you very much Burt for sharing this information with us.

BG: Tom, thank you so much.

25. LOUIS A. GOTTSCHALK

TB: This will be an interview with Dr. Louis Gottschalk²⁷ for the archives of the American College of Neuropsychopharmacology. It is April 6, 1999. We are in Nashville, Tennessee. I'm Thomas Ban. Please tell us when and where you were born and something about your education and early interests.

LG: I was born in St. Louis on August 26, 1916, the third of four sons. My father was born in the United States, of German heritage and my mother was of French-Swiss background, also born in the United States. I'm a typical mixed ethnic background American. I grew up in St. Louis, where my parents and maternal grandmother taught us to speak French at home. My father was a very gifted man with a law degree who never practiced. As a child, he was taught to be a good musician and artist, who wrote for the St. Louis Post Dispatch, as an art and music critic. He was a gifted violinist and pianist, who composed for quartets, quintets, and even opera.

The joy of being creative influenced my childhood and development. On my mother's side, my Uncle Louis went to Paris to study art and became an architect and builder; so both sides of the family were artistic and musical, although I wasn't very good at those things. Still, my parent's easygoing efforts encouraged us to write or be creative, and that behavior was imprinted.

TB: Could you tell us something about your education?

LG: I was growing up in the depression years, 1928-1934, and my older brothers got to go to college, but by the time I came along, the family didn't have any money, so I went to a public vocational school, learning secretarial skills and accounting. When I did finally go to college, I had a lust for knowledge. I felt deprived and eager to learn. I went to night school at Washington University but didn't know what I wanted to do. I was interested in everything that came along, whether it was English or Science.

TB: What did you major in?

²⁷ Louis A. Gottschalk was born in 1916 in St. Louis, Missouri. Gottschalk earned his M.D. at Washington University in St. Louis and his Ph.D. from Southern California Psychoanalytic Institute. He had an internship in Medicine and residency in Neuropsychiatry in Barnes and McMillan Hospitals and post-graduate training in electrophysiology in the Neurology Department at Washington University. Following this, he served in the U.S. Public Health Service in Fort Worth, Texas and in the Intramural Research Program of National Institute of Mental Health in Bethesda, Maryland. He subsequently held faculty positions at the College of Medicine, University of Cincinnati. He was the founding chairman of the Department of Psychiatry and Human Behavior at University of California Irvine College of Medicine. Gottschalk died on November 27, 2008. He was interviewed in Nashville, Tennessee on April 6, 1999.

LG: I had a major in Biology, Psychology, and English.

TB: A triple major. Was there anyone else in the family with an interest in science?

LG: My father had an interest in science and his younger brother, Victor, had a Ph.D. from the University of Chicago in Physics. So, the family was interested in both Arts and Sciences. It probably brushed off on me.

TB: Obviously, it did. After college, did you go straight to medical school?

LG: Yes.

TB: So you did not have any delay between college and university?

LG: No, but I was delayed from high school going to college, because of financial reasons.

There was a two and a half to three year lag. In that period, I was a clerk in the First National Bank of St. Louis and did a lot of other things. It was good for me; I was more mature and really motivated to go to college.

TB: Where did you study medicine?

LG: At Washington University in St. Louis.

TB: An exceptionally good school.

LG: I didn't realize how good it was, but I was certainly inspired in medical school. As an undergraduate at Washington U, I had some outstanding professors, like Frank Webster and Dana Jensen in English, Victor Hamburger, in Experimental Embryology, who probably should have won a Nobel Prize. I also had Holly Compton, a Nobel Prize winner in Physics. There were seven Nobel Prize winners at Washington University Medical School, they were inspired and it brushed off on us.

TB: Could you give us the names of the other two, and also, for what did Holly Compton get the Nobel Prize for?

LG: He was a physicist. I can't say why he got his prize. At medical school, there were the biochemists Carl and Gerty Cori; and there was a physiologist, James Erlanger. They were not only fine researchers but very enthusiastic.

TB: When did you decide to enter psychiatry?

LG: The only reason I went to medical school was to be a neuropsychiatrist.

TB: I see.

LG: I don't know exactly how it happened, but I was interested in the mind and brain and why people behave the way they do, to learn about why they think the way they do.

TB: You had contact with many exceptional people. Did any of them have a special impact on your development?

LG: I should flash back to my undergraduate years. There were some great professors, like Victor Hamburger, who taught biology and experimental embryology, John Paul Nafe, who taught physiological psychology, and a woman geneticist, whose name I can't recall. But my contemporaries, my classmates were important, also. I was surrounded by a group of unusually gifted people, although I didn't realize it at the time. There were people in my class such as Tennessee Williams, William Inge, another playwright, Josephine Johnson, a Pulitzer Prize winner, Ed Meade, who wrote *How to Succeed in Business Without Trying*, and his younger brother, Walter Mead. They were mostly English majors. I wrote for the college magazine and I enjoyed the fun of just writing or "creating."

TB: Did you have any contact with Tennessee Williams?

LG: As an undergraduate only.

After college I wouldn't have had the means to go to medical school, but I got a break. I met the acting head of the Department of Neuropsychiatry, Dr. David Rioch, an extremely gifted neuroanatomist and neurologist, who wrote the section in *Gray's Anatomy* on the extrapyramidal system. He got me a job at Washington U in the Department of Neuropsychiatry; it was a combination of neurology and psychiatry and I also had a Josiah Macy Foundation Fellowship that paid seventy-five dollars a month. That made it possible to go to medical school but I was probably the only one in the class with an outside job. I can visualize all those people I worked with. There was David Rioch, who was doing research. I was assigned to Felix Deutsch, M.D., a famous doctor. His wife, Anna Deutsch, was a famous psychoanalyst, who wrote on the psychology of women. There was John Whitehorn, who became chair of the department. He was a psychiatrist, who had done biochemistry and developed a test for chlorides. There was another person from Yale University, Dr. Edwin Gildea, who had a degree in biochemistry, as well as psychiatry, who later became chairman. Then it was George Bishop, a physiologist, who set a rare example. He was interested in nerves and skin and tested his own hand and arms for all the points where you feel temperature, touch, or pain and then dissected each area. He was credited for discovering and

describing the peculiar little receptors and organs for those sensations in the skin. I had a couple of assistant professors from Harvard, George Saslow, who later became chairman of psychiatry at Oregon State University, and Daniel Badal, who later became professor at the University of Cleveland. Those young men competed with one another for the opportunity and time to teach us, just a few psychiatric residents.

TB: It had to be very stimulating.

LG: Very stimulating!

TB: I assume you went from medical school straight into psychiatry?

LG: You had to have a year of internship; because I was an honor student, Phi Beta Kappa and Alpha Omega Alpha, I was offered an internship in surgery or medicine. I took the internship in straight medicine. It was competitive. The Chairman of Medicine, Dr. Barry Wood, a very good professor, later became famous. After I took straight medicine, I was invited to stay on as a resident, but I was still hooked on neuropsychiatry, and turned it down although the offer was a great honor.

TB: So, after an internship in medicine you went into psychiatry. Weren't you the Chief Resident at a certain point?

LG: I became Chief Resident.

TB: After you completed training in neuropsychiatry, you started in psychoanalysis, didn't you?

LG: I really started in psychiatry and neurology; and it was only later that I got into psychoanalysis. I went to medical school from December 1940 to 1943; they speeded up the time required for medical school and residency training during World War II. We had no summer vacations and the last year we were drafted into the military but were deferred so that we could finish medical school and then serve. I completed internship in medicine and neuropsychiatry residency and then, as soon as they could, they put us to work in our specialty. There were lots of neuropsychiatric casualties, and in 1946 I was at the United States Public Health Service Hospital in Fort Worth, Texas, a 2000-bed hospital on ten thousand acres. It had been a narcotic hospital, turned over to the Navy and Marine Corp, Coast Guard, and Merchant Seaman for neuropsychiatric casualties. I was there for two years. We each had huge patient loads of about a 120 patients, about 30 new patients a month. Around that time, the federal government and the Public Health Service were planning the Institutes of Medicine and the National Institute of Mental

Health. Because I was a hard working public health service officer, the administrators in Texas and Washington DC thought I might be a good recruit, as a psychiatrist, at the National Institute of Mental Health. When the buildings weren't ready in Washington DC, they said I could have another two or three years of training, anywhere I wanted. At that time, I had neurosurgical training in mind, probably because of the example of one of my younger mentors, Dr. Daniel Badal, who did that before he switched over to neuropsychiatry at Harvard. At the same time, of one of my older mentors, Ed Gildea, said it wouldn't be a bad idea to get some psychoanalytic training. When I applied to the Chairman of Neurosurgery for a neurosurgical residency at the Illinois Neuropsychiatric Institute in Chicago, I told him that I would like to enter psychoanalysis as well. He was doubtful whether neurosurgery and psychoanalysis were compatible and turned me down, even after I pointed out that the Public Health Service would pay for the training. So, I went to see Roy Grinker, a famous neurologist and psychiatrist, and he offered me training in child psychiatry. That's how I got into child psychiatry. I did psychoanalytic training, beginning around 1948, in adult and child analysis, at the Chicago Psychoanalytic Institute. In that setting, being interested in the brain and the mind at the same time, were not incompatible. Grinker was a famous neurologist, who had his psychoanalysis with Sigmund Freud. The University of Illinois and University of Chicago both gave doctorates in Neurophysiology and for some reason didn't see any incompatibility between psychoanalysis and neurophysiology. People were involved in both, so I was exposed to that.

TB: Before moving any further, it seems we skipped some of the research you did in the mid-1940s. Am I correct that sometime early in your professional career, you did some research in psychophysiology and published at least one paper? When was that and what did you publish on?

LG: It was published in 1946, in *Psychosomatic Medicine* and it was on producing conditioned vasomotor responses in human subjects, using photoelectric plethysmography. It was done at Washington U. One of my professors, Carlyle Jacobson, a physiological psychologist, got me to read all I could about Pavlovian conditioning and behavior, so that's how I got into the project. But it was also carried out under the influence of Felix Deutsch. I was his research assistant and he had a photoelectric plethysmograph, a device that measured blood flow in the finger. I got the idea, on my own, to see whether the peripheral vascular system could be conditioned, that is whether I could produce vasoconstriction in the fingers in response to a faradic stimulus. I was

also interested to see whether there was any difference between people who condition rapidly and those who don't.

TB: What was your unconditional stimulus and what was your conditional stimulus?

LG: A faradic stimulus was the unconditional stimulus and a light on the ceiling, the conditional stimulus.

TB: So, you conditioned vasomotor constriction to light?

LG: Right. I found that among ten individuals, some conditioned very rapidly, after one or two reinforcements, and some subjects were very hard to condition. I think it probably shows that there are some of us with a genetic propensity to have conditioned vascular responses.

TB: So, you found that people differ in their propensity to acquire a conditioned vasomotor reflex.

LG: I also had a questionnaire to study the feelings of people associated with the vascular response. The subjects who had more variability in their emotional responses were more easily conditioned. I did figure that my findings indicated that some of us have a higher vulnerability to vascular disturbances than others.

TB: What was the hypothesis you tested?

LG: The hypotheses were: can vasomotor conditioning be achieved in human subjects; and are there any differences between individuals who condition rapidly and those who don't. When I was reading Pavlov, I saw that some dogs got easily conditioned to salivary response and some didn't. I wondered whether that happened in humans as well.

TB: Did you link conditioning to temperamental types, as he did?

LG: No, I used a two-tailed test to see whether there was any statistically significant difference. If I found any I knew there were differences between the two groups in temperament.

TB: I suppose you did everything yourself in that study.

LG: Yes. I had to do it all myself while I was working as a house officer and attending medical school. I was in a cordial environment and the department of psychiatry fostered my doing that research.

TB: What year did you actually join NIMH?

LG: In 1951, I was the first research psychiatrist at NIMH.

TB: With whom did you work and whom did you recruit?

LG: I wasn't into recruiting; but I can tell you who was there.

TB: Who was there?

LG: The Institute was run by a doctor who had been, for a short time, at the United States Public Health Hospital in Texas. His name was Dr. Robert Felix.

TB: The first director of NIMH?

LG: He was the first director and I was the first research psychiatrist. There was a neurophysiologist, Wade Marshall, Ph.D., who learned that when I was in Chicago, I had done studies with epileptic children, and he thought he could collaborate with me. He wondered whether I wanted to irritate the animals in order to have seizures, while he placed aluminum gel on their brains to make them more susceptible. I declined, knowing I was free to do whatever research I might want.

TB: Whatever research you wanted to do?

LG: Yes. It still works that way, I think.

TB: Am I correct that you were involved in EEG research in those days?

LG: While I was at the United States Public Health Service Hospital, they wanted somebody to run the EEG laboratory in the department. They let me go back to Washington U for a couple of months to learn more about electroencephalography. I already knew some, but I focused on it for a couple of months with James O'Leary and George Bishop. That was a relatively new procedure back in those days. Then, when I transferred to Michael Reese Hospital, I got involved with their EEGs; reviewing them. It was there that I asked the Clinical Services for Children to see some of the kids, in whom anticonvulsant medication didn't control their seizures. I saw a number of these children and decided to treat a selected few with psychotherapy and/or play therapy. One of my first control cases in child analysis was a five year old Polish Catholic boy, who had seizures, not inhibited by anticonvulsant medication of any kind. It was then I got the idea to see if analysis had any favorable effect. That's how I happened to get into research into the psychological trigger mechanisms of epilepsy. I think I wrote that up somewhere. That little boy did get better; his seizures stopped. I saw him about four times a week and did very classical psychoanalysis. I followed that case for many years. There's another child I saw, an eight year old boy, in whom looking through a window screen could bring on a seizure. I wrote his case up and published it in the *Psychoanalytic Study of the Child*. From that experience I got the idea of looking for the trigger process of seizures in kids and won the Hofheimer Prize for Research in Psychiatry.

TB: What year did you get the Hofheimer Prize?

LG: This was probably in 1955.

TB: So you got the Hofheimer in the mid-1950s and started your work in children whose seizures were not controlled with anticonvulsants before you moved to NIMH. What did you do at NIMH?

LG: When I arrived at NIMH, I asked myself what I am going to do. I decided that I would try to continue working with epileptics, and it happened that Dr. David Rioch, who had been one of my mentors at Washington U, was now head of neuropsychiatry at Walter Reed Army Hospital. I decided I should look him up to tell him what I wanted to do. He made it possible to study inpatients with recurring abnormal EEG paroxysms and EEG waves, who might or might not have visible seizures, and to interview them. This was an attempt to combine free association with neurophysiologic findings and I did that for some time. I did find the right kind of patients and I still have records of them. It was easy to identify the abnormal EEG paroxysms, they were very clear-cut. The other side of the research, listening and recording what they said, wasn't very objective.

TB: What was the pharmacological treatment of epilepsy in those years?

LG: There were a variety of anticonvulsant medications, including phenytoin (Dilantin) and the barbiturates.

TB: How long did you stay at NIMH?

LG: From 1952 to 1953.

TB: Where did you go from NIMH?

LG: To Cincinnati. I had two children and was married to a very gifted and beautiful doctor, Helen Reller. She was a dermatologist; we were very happy and wanted more children. But even though we were both well trained and had American Boards in our medical specialties, I had a relatively small income. When I asked my superiors whether it would be possible for me to do private practice to supplement my USPHS salary, they wouldn't let me. I was offered a position at the University of Cincinnati; at that time, the University and Cincinnati General Hospital was one of the top places for psychosomatic research. They had some famous people there.

TB: So, you moved to Cincinnati, in 1953. Who was the Chairman of the Department of Psychiatry?

LG: Maurice Levine. There were other people of scientific note; Arthur Mirsky for one.

TB: Wasn't Paul Ornstein there as well?

LG: He was just a psychiatric resident, when I first went there, and not that famous yet. But, Arthur Mirsky was there, and George Engel. It was a congenial place for psychosomatic research. I was into that. Later on, I became Paul Ornstein's training analyst and knew his wife, Anna Ornstein, who had been in a Nazi prison camp.

TB: Douglas Goldman was also there and was involved with psychopharmacology. Did you know him?

LG: Very well, sure. But he wasn't on the faculty in the Department of Psychiatry. He was in the forefront of drugs, using them a great deal, but not in a discriminating way. He didn't use placebo controls in his studies; he was an enthusiast, who didn't do hard experimental work.

TB: Yet, as you said, he was very much involved in pharmacotherapy with psychotropic drugs. He was a great clinician and had a large practice. He was in the forefront with chlorpromazine and some of the first psychotropic drugs. That was not as popular at that time. LG: Arthur Mirsky was a biochemist, interested in psychoanalysis; he made some interesting contributions and went to the Chicago Institute of Psychoanalysis.

TB: It seems there were many interesting people in Cincinnati to collaborate with?

LG: Yes. George Engel was another. He was an internist who also got interested in psychoanalysis. He had an identical twin who he outlived.

TB: What was your position in Cincinnati?

LG: At first, research associate professor; and later, research professor.

TB: It is from Cincinnati that you moved to Irvine?

LG: Yes.

TB: Where did you start your research on content analysis of speech?

LG: At NIMH, where I had the luxury of doing any research that I wanted. It was a researcher's dream and I decided we needed to objectify the diagnosis of mental states or psychological feelings from language. Having looked at free-associations and abnormal EEG paroxysms, I got the idea I should try to use language and see whether I could objectify the mental state from that. I started out with a younger colleague, Gove Hambidge, taking movies of people. We tried to put everything together; movement, tone of voice, what they said, and the semantics.

I realized this was more than was needed. But our work was published; we did a couple of papers together.

TB: Did I understand the name of the young colleague you collaborated with was Gove Hambidge?

LG: Gove Hambidge had also been at the United States Public Health Service hospital in Fort Worth, Texas, and was also given the opportunity to go to NIMH. He had been a graduate of Yale Medical School, and while at NIMH, they let him have psychoanalysis in New York City. After I started at NIMH, he joined me six months later. I stuck to working on the content analysis of verbal behavior, but he left and never did go back to it. TB: Then, you continued your research in content analysis in Cincinnati?

LG: Yes, having been at NIMH, I knew that applying for research money is not easy. But, I applied for various research grants and got some. Among them, was a grant on content analysis of language. Later, in about five or six years, when I was getting some prominence in research, I obtained a Research Career Award. It wasn't a lot of money, but it allowed making a living with four kids and doing some research.

TB: So, you got into your research on content analysis of language because you felt there was a need to objectify mental status. Why did you choose content analysis to achieve that objective?

LG: I like to write. I like to listen to language. I was interested how do psychiatrists learn anything about anybody? They do what you're doing now, asking questions, listening, and trying to make something of the language. I had some interest in language, including foreign languages. I spoke a bit of French and I studied German; languages interested me. I was also interested in the way skillful people arrive at conclusions about how somebody else feels. In Chicago, they often argued about that. I had a mentor in Chicago, Franz Alexander, a fellow Hungarian, a countryman of yours. He and other people used to argue about what a person was communicating and I wondered why do they have to argue? I found out later they just liked to argue, even when they agreed. In any case, I think that got me into language analysis and I stuck to it. When you're trying to make an assessment of somebody's feelings, or a diagnosis, you can use a psychiatric interview, an adjective checklist, a Beck Depression Inventory, or some other assessment instrument. I was wondering whether one could have something more scientific, since people differ a lot in how they respond to adjective checklists. The reliability of checklists is pretty poor. That pushed me on to

see whether I could improve on the measurement problem. I had no idea that it would go as far as it did. I think it was a wise choice I made twenty-five years ago; we proved we could do content analysis of language, made headway in reliability and validity, and computerize the methodology. That was a lucky thing, or maybe not just lucky; it took so damn much time to try to figure out how to score the scales, according to the “Gottschalk-Gleser Method,” that it was like having to go back to school. I thought, if it can be done by a human, it should be possible to do it by machine. So I stuck to that. The first grant I applied for this, from NIMH, in 1975, was turned down. The pink sheet said it’s impossible to do this by machine.

TB: But you succeeded in quantifying content analysis of language and computerizing it. LG: The same interest in getting numbers was involved when I went into pharmacokinetics and determination of drug blood levels.

TB: You were interested in quantifying whatever you studied?

LG: Exactly. Blood levels, content analysis of language, brain waves; you can measure and quantify them all.

TB: You were also interested in drug and personality interactions. You had a paper way back with a title, “An exploration of testing drugs that effect mental activity.”

LG: That paper was published in JAMA, in 1956.

TB: What was the drug you were using?

LG: It was pipradrol. Do you know it? Very few people are familiar with it any longer.

TB: Yes, I worked with it in psychogeriatrics.

LG: I tried to measure the reaction of people to small doses of the drug versus placebo. I got a group of pharmacologists and psychoanalysts involved. The interesting finding was how personality affected experience of the drug. People who were uncomfortable being pushed to do something, instead of getting a pleasant feeling, got anxious, whereas people who were depressed or liked to feel pushed felt better. The range of reactions to small doses of pipradrol was large and depended on the personality of the subject.

TB: Was that your first paper in psychopharmacology?

LG: Except for the paper I published on those kids in Chicago, whose seizures were not controlled by anticonvulsants. In that study, I was motivated to find out whether they had incorrigible seizures

or there was something else triggering them. With pipradrol, I studied personality and drug interaction.

TB: In the pipradrol study, did you use any test to measure personality?

LG: No, I simply asked the subjects what their emotional reaction was.

TB: So, there was no special testing procedure?

LG: The questions I asked are documented precisely in the article. At the time I did that study, I was already developing the content analysis methodology. I tried two approaches in content analysis.

TB: Two approaches?

LG: One approach was just looking at words, whereas the other was looking at words with their meaning as they were communicated in a whole grammatical clause. Using the first approach counts only the number of representative adjectives or verbs and so on. I published some rather interesting papers using that approach. In one study on suicide notes, I demonstrated that you could distinguish real from false suicide notes. That was a study organized by two suicide researchers. We published our findings with the title, "Are there any differences in false and genuine suicide notes," in *Medical Psychology*. There was a difference in the use of words. I wondered whether I should stick with that approach or look at the grammatical clause, the smallest unit of verbal communication. I later decided to focus on the grammatical clause because with semantic units, the smallest is a grammatical clause. If somebody says "damn" it means usually "damn you," but taking words out of context can be unreliable and does not provide objective and valid findings. There was a group at Harvard that used just words. But the meaning of words depends on how they're placed in a sentence. For example, there's a "damn you" or "damn myself." Just counting the words does not tell who is angry with whom. So, I stuck to the grammatical clause.

TB: Speech and content analysis is central to your research, and one of your important contributions that historians will be interested in. Could you describe for me what you were using to arrive at a reliable and valid assessment?

LG: I'll give it a shot. This remains a problem, although I've been publishing in the area for 25 years. The whole process has grown, so it's got more and more complicated and when I try to explain the procedure, and how you can teach a dumb computer to do it, it is rather difficult. If

someone is interested in the details, they should go to the original writings. But let me give it a shot. How can one measure the magnitude of anxiety, the severity of schizophrenia, or cognitive impairment from five-minute speech samples? One problem is how can you standardize what somebody says? This was the first step and to do so we borrowed some ideas from psychology, namely from projective testing, specifically from the Thematic Apperception Test. We developed a standardized way of eliciting speech and these were the instructions: "This is a microphone to study speaking and conversational habits. I would like you to talk for five minutes about any interesting or dramatic personal life experiences you've had. While you're talking, I would prefer not to reply to any questions you might have until the five minutes is over. You can talk about one experience and if the five minutes is not over, you can talk about another. Do you have any questions now?" The subject might ask, "What is interesting or dramatic?" The answer was: "I don't know what's interesting and dramatic as far as you're concerned, don't worry about me, just whatever you think," purposefully turning the question back to the speaker. "Do you have any questions now?" If the subject said they did not, then the interviewer said, "All right you can start now, and then, in five minutes, I will tell you to stop." To get a reliable sample, a person had to speak at least 85 words. Less than that in a five-minute period, the sample wasn't good enough. It's just like getting a blood sample; if the sample is too small the results may not be reliable. The speech samples were recorded and the transcript typed in text, ASCII or Wordperfect 5.1, and lately, in Microsoft Word, because the artificial intelligence software program, LISP, is programmed to understand these computer programs. The speech sample was scored after it was typed up and punctuated with the insertion of periods and commas. The program needed help in case of a compound sentence that had to be separated by a comma. So the typist put in a slash or diagonal to tell that a clause had occurred. Now our software program recognizes and does all this clausuring by itself. The key question is, what do you examine in the sample? It qualifies the word and examines its meaning. The program is doing that by understanding all "parsing." Parsing is a capacity to label each part of speech, as noun, pronoun, adjective, verb, adverb, preposition, conjunction, and so on. All that information, over 200,000 words, has been put in the memory of the computer, to teach it the words and their meaning. It knows that a word like "hide" can be a verb, or it can be a noun. It also knows there's a difference between, "He hit me" and "I hit myself." It makes a difference in psychiatry whether you're going to conclude, "I like myself" or "I hate

myself” or “Somebody doesn’t like me.” In addition to having the semantic knowledge of over 200,000 words or idiomatic phrases, the computer knows every slang expression. If somebody says, “I’ll kick the bucket,” it knows that doesn’t mean somebody literally kicked a bucket, but it means somebody is going to die. It has, in its dictionary, every slang expression one can think of. We keep adding to the program’s dictionary when we hear another commonly used word or expression that merits addition. Take a phrase like “it sucks.” Under certain circumstances that means something isn’t good, but if you say, “the baby sucks,” that’s different. If there is ambiguity, the program first searches out the meanings of the words it has in its memory that for example, could fit into the anxiety scale. The scale is divided up into six sub-scales; death, mutilation, separation, guilt, shame, and diffuse anxiety. For example, it recognizes “I’m nervous and I feel guilty,” as guilt anxiety, and “I was embarrassed,” as shame anxiety. Now, the computer dictionary has learned from somebody, mainly from me, to classify every word and how it can be used. I may have missed some words or classified them wrong, but the computer, in contrast to you and me, is consistent and keeps making the same error. So, the first thing the computer does is search for the meaning of each word and how it fits in the scales. If a word can be classified in several scales, it registers that. Then it searches who did what to whom, because that makes a difference. After it registers all the possibilities for each word, it decides how to classify and score them. It compares, adds, and tallies, all verbal statements, because somebody could say something hostile to others and to themselves, as for example “I shot myself in the foot and also, shot him.” It may score some statements on several scales and it adds all the scores up. Then, it compares those scores to norms. We got the norms by getting verbal samples from thousands of people for the different scales. These people were working, as well as mentally and physically healthy. And the norms are adjusted to the educational level. If you have a verbal sample from a five-year old kid and from a Princeton college graduate, they’re going to be differences in cognitive function. So, the software program makes adjustments for that. It also calculates standard deviations from the norms and tells you what they are. It’s more reliable, if you have more than a five minute sample but the computer is programmed to provide a disclaimer about that. This allows a clinician to consider the diagnostic classifications derived from a verbal sample for the diagnoses in the DSM-IV of the American Psychiatric Association. That wasn’t a very good summary on my part, but it should give you a general idea.

TB: What you have in the development of the program is a logical process.

LG: Gradually, it aims to be logical.

TB: Gradually?

LG: If you live long enough, you can do a lot; and I've lived pretty long. We did studies, years back, when we had a NIAA Alcoholism Research Center, on how well we could take five minute verbal samples and develop regression formulas that provided neuropsychological tests scores from the Halstead-Reitan Cognitive Scale. The program printed out if the cognitive impairment score was more than one standard deviation from the norm.

TB: Let me go back to Cincinnati. You moved there in 1953, just before chlorpromazine and reserpine were introduced. And you were in Cincinnati when meprobamate, imipramine, and the benzodiazepines entered the psychiatric scene. Central to your research was the development of content analysis of language, but you also became involved with research in psychopharmacology. How did that happen?

LG: I could say it just happened, but usually things happen for a reason.

TB: It was just a couple of years after you moved to Cincinnati that chlorpromazine was introduced.

LG: A magic drug.

TB: How did you feel about it?

LG: I was very enthusiastic. It worked, it really did.

TB: But you were not involved in clinical research with it.

LG: I didn't publish, but I was a psychiatrist at Cincinnati General and used it. As I said, it worked.

TB: Did you have any experience with reserpine?

LG: We used it, surely.

TB: What about meprobamate. Did you use it?

LG: We used all of these drugs. I was on a busy clinical service.

TB: Were you involved in research with any of the new drugs in the 1950s and 1960s?

LG: I don't remember exactly, but I did some research with perphenazine and some of the benzodiazepines.

TB: Could you tell us something about the research you did with perphenazine?

LG: We had a busy clinical service and put several patients on perphenazine. I wanted to see whether the content analysis scales were useful. I was developing scales around that time that measured three types of hostility; hostility outward, hostility inward, and ambivalent hostility.

Perphenazine suppressed all three types of hostility.

TB: What about benzodiazepines?

LG: I worked with chlordiazepoxide first. I thought that chlordiazepoxide should lower the anxiety scale scores significantly more than placebo. The major focus of my research was not as much testing the drugs but testing the scales. I wanted to know whether they measured what they were supposed to measure. But, as I reflect on it now, I certainly was interested. Later, I did studies with diazepam, lorazepam, and triazolam.

TB: Did you study triazolam on sleep?

LG: No. Just generally to see what, if any, effect it had on the content analysis scales. I was interested in the effects of these psychoactive medications on the scales we were developing, and in the relationship between their blood levels to the magnitude of our scale measures. I found out they were capable of measuring what they purported to measure.

TB: So, you were using psychoactive drugs in the construct validation of your scales?

LG: Exactly.

TB: Did you do any research with antidepressants?

LG: I did some research with imipramine. In one study with non-depressed patients, imipramine reduced the hostility level of subjects. TB: So, that study was done on normal subjects?

LG: Pretty normal. Then, with amphetamine and a mild barbiturate, we were trying to see whether these drugs could overcome what the doctor said.

TB: What did you do and what did you find?

LG: We did a placebo controlled study. After we told the patients we were going to give them a drug to make them sleepy, we gave some the amphetamine, and after we told others that we were going to give them a drug that would stimulate them, we gave the barbiturate. We had devised an instrument we called "Achievement Striving Scale" and showed that amphetamine overcame the effect of what the doctor had said. But we also showed that there was an effect in response to what the doctors said.

TB: Have you been involved in research with any neuroleptic other than perphenazine. Didn't you do some research with thioridazine?

LG: Yes, but later. I got involved in research with thioridazine and had some grants for that, but that research on thioridazine and mesoridazine was done in California. I studied first the pharmacokinetics of thioridazine, and then, when I got into the metabolites, I detected that one of them, I think it was sulforidazine or a sulfoxide, was probably responsible for the adverse effects on cardiovascular function. Sandoz, the pharmaceutical company that made these drugs, gave me money to study thioridazine, but when I said I wanted to find out how to reduce the amount of metabolite that caused the cardiac effects, they didn't want to fund it.

TB: Thioridazine was the first neuroleptic in which the prolongation of QT interval on the EKG caused problems. In the early 1960s, a couple of patients treated with thioridazine in a mental hospital in Kingston, Ontario, died of ventricular fibrillation.

LG: Is that right?

TB: Yes, it was quite carefully followed up in controlled studies and Sandoz knew about it. Why didn't Sandoz want to fund your study?

LG: I don't know.

TB: You certainly made an important contribution by identifying the metabolite possibly responsible for the quinidine-like effects of the drug.

LG: Everybody told me that metabolite was not pharmacologically active. I asked the head of the organic chemistry department at UCI whether she could manufacture it for me, because I wanted to test the effects of the metabolite on cardiovascular function in dog experiments. She could do it for a certain amount of money, but I never was able to obtain the necessary funds. In general, pharmaceutical companies are not very interested in trying to discover what triggers the adverse side effects of drugs. I was interested and I still am. It's a neglected research area, in spite of the fact that it could help to avoid some adverse side effects. But the drug companies just don't seem interested.

TB: How did you identify the metabolite that is responsible for the cardiac conduction changes?

LG: We got regular blood levels of all the metabolites from patients that were taking thioridazine. We would get EKG's and look at those patients that had higher levels of the metabolite. Not everybody metabolizes these medications the same way, and we found that patients with higher

levels of that metabolite had abnormal EKGs. Our research focused on drug metabolism and we discovered some metabolites of drugs that other people never reported. That got me pretty far off the main direction of my research, but I had a young collaborator, Eugene Dinovo, out of UCLA, and he loved that kind of research. We had a great time collaborating. There should be more studies like that; it's an open field, the study of adverse side effects of drugs and metabolites.

TB: Did you discover any other metabolite of a psychotropic drug linked to an adverse effect?

LG: No, but we had problems funding that area of research. Eugene was a bench researcher, on soft money, so I had to keep getting grants to fund him. Eugene was brilliant and is probably still working as Director of the Pathology Lab at one of the VA Hospitals. While we worked together, we discovered some other metabolites which are not in the scientific literature. We didn't try to see whether they were related to anything, because we didn't have the necessary funds. When you have federal grants, you can't go too far off, because you've got a responsibility to focus on the principal goals of your research.

TB: You think some of those findings should have been followed up and were not?

LG: Yes, I want to pursue a lot of interesting things, but I have to decide my first priority.

TB: It's unfortunate that you couldn't pursue your research further with the thioridazine metabolite.

LG: I visited Sandoz in Basel a couple of times. I'm sure their higher ups advised them not to spend money on that line of research because they were doing all right with the drug. You can't get a pharmaceutical company to study what triggers the adverse side effects of their drugs. I may be wrong.

TB: The thioridazine induced cardiac conductance changes are of special interest to me because we were the ones who demonstrated that thioridazine could induce prolongation of the QT interval and ventricular fibrillation in the therapeutic dose range. We published our findings, I think in 1964.

LG: I didn't know that.

TB: Let's get back to your research in Cincinnati. Didn't you do some research in hypertension?

LG: I studied the effect of hydrochlorothiazide on hypertensive patients and found it had not only an effect on hypertension but also on the subjects' language.

TB: Did the effect on blood pressure and speech correlate?

LG: Yes. Around that time, it was more and more convincing to me that we had a useful and valuable measure of anxiety and hostility in content analysis. I thought I'd like to validate it some more, with respect to a combination of biochemical and physiological factors that could be measured including a blood sample. At that time, there was not a good measure of adrenergic substances such as epinephrine and norepinephrine that were thought to be involved in influencing states of anxiety or hostility. We could measure only plasma free fatty acids. These are released from the liver and fat storage in response to a chemical substance that's secreted in the blood stream, in association with the arousal of anxiety, fear, or anger. So, I decided to measure plasma free fatty acids, and we did a number of studies in which we showed that the higher the anxiety levels in normal individuals, the higher the plasma free fatty acids. What we were measuring in verbal samples as anxiety or fear was associated with the biological release of adrenergic substances. We did a lot of other studies using that technique. As I said, it was the only measure in those times that was available. And, we noted, subsequently, that if we drew blood from a subject before and after taking the five minutes speech samples, the free fatty acids went higher with their anxiety; the more anxious they were during that five minutes, the higher their free fatty acids were. We also noted that in dreaming subjects, if you drew blood from them at the beginning of rapid eye movement sleep, and fifteen minutes later, the higher the anxiety in the dream on my anxiety scale, the higher the free fatty acids went. The article in which we reported these findings was published in *Science*. I had an interesting query in answer to that paper from a number of people. One scientist commented, "If there's more anxiety in dreams, there's more arousal of adrenergic substances and in some instances that could be fatal, just from a dream." Another query I thought was amusing was, "Why not recommend that everybody get psychoanalyzed and put an end to anxiety dreams?" I had to write back that psychoanalysis doesn't put an end to anxiety dreams, but a person might understand better what the anxiety was about.

TB: You certainly did more than simply correlating anxiety with plasma free fatty acid levels.

LG: We confirmed that anxiety measured from language was associated with physiological, neurobiological, and biochemical concomitants in the body and wasn't just a matter of the mind. When you ask me these questions, I get a flood of memories. We noted that people in Cincinnati that were into sports, had all around lower plasma free fatty acids, than people who were not involved in sports. That's a popular belief now that a certain amount of exercise is good for the

body, as well as for the mind. I do recommend to patients once in a while, “Healthy Body, Healthy Mind.” There’s something to it. We looked at blood cholesterol, also, and found that the higher the hostility scores, the greater the blood cholesterol in normal subjects. There is no paper published on that, but there is a lot of preoccupation these days with elevated cholesterol. In the 1960s, we didn’t look at whether LDL or HDL cholesterol was elevated. We were just getting total cholesterol. I don’t think clinicians were thinking very much about other factors in those days.

TB: So, you were very involved over 30 years ago in measuring cholesterol, free fatty acid, and triglycerides?

LG: Yes. That was part of being in the Cincinnati environment. As I said, there was lots of interest in psychosomatics; we were looking at what effects emotions have on the fatty acid and triglyceride metabolism. I haven’t gone back to that area of research since Cincinnati, but I noticed that in the current literature, there’s some interest in it.

TB: Did you study the effect of drugs used in the treatment of anxiety on cholesterol, free fatty acid, and triglyceride levels?

LG: We did that in the course of our research with the β -blocker, propranolol.

TB: What did you find?

LG: I found that β -blockers do, indeed, decrease anxiety levels in content analysis scales, and decrease plasma free fatty acid, but not significantly. Since I was seeing these responses, partly as a measure of the peripheral autonomic nervous system, I concluded that anxiety was primarily a central nervous system phenomenon. Of course, our findings didn’t prove that it couldn’t be peripheral because we used a β -blocker that doesn’t go through the blood-brain barrier. Anyway, our paper on propranolol attracted the attention of Bayer, a large German pharmaceutical company, and I was invited to an international meeting of cardiologists in Venice, where I presented our findings because cardiologists were interested in the details. It was a marvelous experience. Later, my presentation was published in a book chapter on β -blockers.

TB: In your conclusions in the propranolol paper, you said also that the anxiety you were measuring was primarily a central nervous system phenomenon, but you couldn’t exclude the possibility that it was peripheral. Can your content analysis of language differentiate between fear and anxiety, or between two kinds of anxieties, as some people do?

LG: I don't think my content analysis differentiates anxiety, which is sometimes called "neurotic fear," from "genuine fear." It's measuring arousal whether it is neurotic or real fear.

TB: So, it gives a single measure of anxiety.

LG: Yes, anxiety and fear.

TB: Let me shift to another interesting project you did in Cincinnati. This is your study of neuroleptic withdrawal in chronic hospitalized mental patients.

LG: It was difficult to do that study, but we did it at Longview State Mental Hospital that had a lot of chronic schizophrenic patients. I got the hunch that some of those schizophrenics seemed pretty normal to me after they had been there about ten years. I think it was the beginning of the time when it appeared there could be adverse effects in patients due to chronic administration of phenothiazines. So, I wondered what would happen if we discontinued them in a group of patients. To do that we had to get the hospital's cooperation and I succeeded. I did the study with 75 patients and found that maybe a third or a half remained about the same or seemed even better, more collaborative. At that time, I was developing a scale for measurement of the severity of schizophrenia. I named the scale, Social Alienation-Personal Disorganization Scale (SAPD). We employed this scale on patients before and after withdrawal of the large amounts of phenothiazines they were on and found out that those inpatients in whom the SAPD score before taking them off the phenothiazine was low were OK if you discontinued medication, whereas patients whose SAPD scores were well above that got very significantly worse. Our findings were of considerable interest at that time. It demonstrated that not all chronic schizophrenic patients had to be kept for the rest of their lives on a major tranquilizer. So, we discontinued the old practice, and a fair number of patients who were off medication for a while could be discharged.

TB: You found that maybe as many as 50% of hospitalized chronic schizophrenic patients probably did not need to be kept on their medication. That was a significant finding.

LG: Exactly. There are either different kinds of schizophrenia, or different levels of severity.

TB: The number of patients you took off medication was around seventy?

LG: Yes, 75 patients.

TB: Did you take them off suddenly or did you gradually decrease their medication?

LG: Abruptly, but we substituted their psychoactive medication with a placebo. It was not easy to do because the hospital personnel, especially the nursing staff, didn't want it done.

TB: Was there any withdrawal effect?

LG: No, we did not see any withdrawal effects.

TB: So you found a relationship between the level of disorganization measured by your instrument, and a need for phenothiazine medication.

LG: Yes.

TB: How did you measure “disorganization” with the scale?

LG: If somebody giving a five-minute verbal sample did blocking, that is started a sentence and didn't finish, that was scored. Not just content, but also the form of speech was evaluated. If they made bizarre statements, like “I saw somebody walking on the ceiling last night,” or articulated paranoid tendencies it was also scored. Verbal items that trained psychiatrists typically use to make a diagnosis of schizophrenia were scored on the scale. The SAPD scale overlapped, later, with another scale that we developed for depression. After all, some people with bad depression can be delusional.

TB: Do you think your scale picks up positive symptoms, or negative symptoms, or both?

LG: When we developed that scale, we found there wasn't a big distinction between picking up positive and negative symptoms; I'm not absolutely convinced that the distinction is important, but if it is, my scales could probably be broken down to differentiate between positive and negative symptoms. I could possibly determine whether there is any difference but haven't got into that. The trouble with that distinction is that some of the negative symptoms might be related to personality characteristics and not necessarily schizophrenic features. For example, if somebody had a head injury, or an addiction, or a lot of shock therapy, I think that might produce some of the findings that are associated with negative symptoms. I'm not sure. And, if I were to study positive and negative symptoms I'd want to get PET scans or MRIs to see how the patients differentiate. There has been data along that line. I think Andreasen and others have shown some differences in the brain.

TB: You went as far as your instruments let you go. You didn't have MRI at the time.

LG: We didn't have MRI, CT, or PET.

TB: This was the Cincinnati period of your career. You were involved in many things and dedicated much of your time to research.

LG: I also had practice, I was a training and supervising analyst, and I had grants. But it's true, I dedicated a lot of time to research.

TB: You moved to Cincinnati, in 1953 and stayed there for almost 15 years.

LG: I left Cincinnati in 1967.

TB: Then you moved to California, Irvine to become the Founding Chairman of the Department of Psychiatry and Human Behavior.

LG: I took the position as Chairman and there was, immediately, a very large administrative responsibility to get an approved residency, to recruit residents, to worry about all the financial problems in running a hospital. We had an emergency room that saw a thousand patients a month. I kept convincing myself that I had to continue to do research, so I knew what my identity was.

TB: So all through the Irvine years, while you were building a department, you continued with your research.

LG: I kept doing research and applying for grants.

TB: For how long were you the Chairman of the department?

LG: About eleven or twelve years.

TB: What percent of time could you spend in research?

LG: Twenty-five percent.

TB: What about clinical practice?

LG: You were allowed two half days a week to practice. You didn't have to do private practice; you could do none, if you had a ceiling to your salary. At the University of California, the pressure was to publish papers. I didn't have a problem there; they have a very fine university system. It is definitely a research university, whether it's humanities, physics, or medicine. It rewards research; it was my type of university.

TB: What about teaching responsibilities?

LG: I tended to do more of my teaching with residents, rather than medical students. I did give a few lectures, but I hired people to teach medical students. I had to build a department from scratch, so I worked up a big residency program. I had fifty or sixty residents.

TB: And you said that you had to spend time writing grants to generate funds for your research?

LG: The University of California was set up for the kind of research I was doing, so you didn't always need a grant. I had a lot of residents who wanted to do research, to get speech samples on various topics. But if you want to do certain kinds of research and want to get a lab, you have to get big grants and I worked for that. But, in between, I was always able to do research. There was a period of six to seven years when I had large contract grants from the National Institute on Drug Abuse that profoundly affected my activities. While serving on different committees of NIDA, and the NIAA, I discovered that there was no uniformity across the United States in the way psychoactive drugs were evaluated by medical examiners or coroners. So I began a project NIDA supported for six or seven years, to develop a uniform system measuring all the variables in drug-involved deaths. We had a team that developed a uniform system and made recommendations. NIDA also gave me funds for a lab where we could check some of the coroners' findings. The data from the studies we did in the laboratory and the information I got from coroners and medical examiners has been stored away. But based on that, in collaboration with Robert H. Cravey, the head of the toxicology laboratory of Orange County, we wrote a book on *Toxicological and Pathological Studies on Psychoactive Drug-Involved Deaths* that was published by Biomedical Publications, in 1980. The book provides the blood levels, lung tissue levels, and all other relevant tissue levels in poisoning and death due to benzodiazepines, opiates, and similar drugs. Many coroners in this country are using our book. My research team and I also had another publication, in 1977 that was prepared on request by the National Institute of Drug Abuse, (NIDA). It is a *Guide to the Investigation and Reporting of Drug Abuse Deaths*. My co-editors of that book were: Frederick L. McGuire, Eugene C. Dinovo, Herman Birch, and Jon F. Heiser. It was published by the U.S. Government Printing Office.

TB: So, that book was focused on identifying the drug that caused the death.

LG: There are interesting legal cases in which it is difficult to determine whether the cause of death was a morphine overdose or too big a shot of insulin injected later. There are interesting cases and a wealth of material for any mystery writer. I don't believe the ACNP ever looked into that matter. Why should it? The drug companies aren't interested in such details. However, I did get involved in this area and I don't regret it. It consumed a lot of my time, but was, I think, a very worthwhile adventure.

TB: There was that famous case of a wealthy woman who was killed by her husband with insulin.

LG: Yes.

TB: Were you involved in any way in that insulin overdose death?

LG: No, but I've been quoted on the possible cause of Marilyn Monroe's death. The findings are given in our book. The question was whether she overdosed, or whether she was killed by the Mafia through an injection in her rear end. I don't want to go into all the details now. Somebody wrote a book suggesting that the cause of her death wasn't suicide, that she might have been killed. I think the experience taught me that when somebody takes a drug, it doesn't have to go just to the brain; it gets all through the body, the liver and everywhere else and pathologists should look to see what the levels are in different tissues.

TB: And while you were involved in that project, if I'm correct, you were also Director of your Drug and Alcohol Center.

LG: The Alcohol and Drug Research Center comes later. I came to UCI, in 1967, and was Chairman of the Department for about 12 years. Then, I became head of the Psychiatric Consult and Liaison Service at the UCI Medical Center. I did that until I became the Scientific Codirector of an Alcoholism Research Center, funded by the National Institute of Alcohol and Alcohol Abuse (NIAAA) that was a conglomerate of basic and clinical scientists. The main theme of our Research Center was "The Effect of Alcohol on the Nervous System." We were looking at humans and animals; we had some powerful research people from molecular biology and neurobiology, and we worked together for about 10 years.

TB: Did you pursue your research with speech samples at the Center?

LG: The Center was getting data on cognitive impairment.

TB: So, after you retired from your Chair, you did some work in consult-liaison psychiatry, and then became co-director of this Center. Didn't you also become Professor of Sociology and Ecology?

LG: Social Ecology and Social Science. Even when I was Chairman of Psychiatry, I had courtesy appointments there, because in a research university setting such as the University of California, it was useful to get cross fertilized and work in several departments.

TB: How long did you co-direct the Center?

LG: Our grant lasted for about eight or nine years.

TB: When was the Center in operation?

LG: In the 1980s.

TB: Could you tell us something about your research in the 1980s?

LG: It was in those years that I did the Reagan Study. There was a campaign debate between Mondale and Reagan. We were studying with content analysis the language used in conversations. We learned that we could study conversations if we looked at the form of speech rather than the content; for example, how many times a person repeats himself.

TB: How did you measure that?

LG: Counting every time there is a repetition of a word or phrase, separated by no more than a word, phrase or clause. It doesn't matter what the content is. Those issues turn out to be important in older people, or people that have brain injury. They are more repetitious, no question about it. It's related to age; little kids also often repeat themselves. It's sometimes related to the vocation. A clergyman, rabbi or politician will say, "I tell you, I tell you that we have to defeat..." They repeat themselves for emphasis.

TB: You started to say that you did the Reagan Study. How did you get to that and what did you find?

LG: About 1984, I was consulted by Gannett Publications from Washington, D.C., after I had been recommended to them by the American Psychiatric Association, in Washington, They were told that I have a content analysis measure derived from speech and they asked me whether I would collaborate with them and measure the relative cognitive impairment in the debaters, specifically of Reagan and Mondale. So, they sent me the tapes and videos of those debates. In a political debate the debater cannot read a prewritten script; they have to be spontaneous and are somewhat unprepared. I received the tapes and the videos of the number one and the number two debates and looked at them myself. I didn't have a computer program to do this at the time, and when I studied the tapes, I noted that when Reagan didn't have a script, he had to freelance to be spontaneous. And, my goodness! His scores on content analysis items for cognitive impairment were significantly higher than Mondale's. So, I told Gannett Publications what I had found. I also asked them for the tapes and videos of some earlier debates that Reagan had with Carter. Those debates were four years earlier. When I was looking at those data, and their content in the cognitive impairment scale, Reagan didn't look as bad as he did four years later debating Mondale. I asked myself, should I publish that? This was before the election and Dr. Bunney, who was the Chairman

of the department at the time, didn't think I should publish it. He was not worried in terms of research but he was concerned that publishing those findings might negatively bias the National Institutes of Health in receiving grants. So I asked the Dean of the College of Medicine, Stanley van den Noort what I should do. And he asked me, "How did it come out?" Well, I said, "Reagan didn't look as good." So, he said, "Publish it!" Well, I said, "Stanley, you're a Democrat." "You bet." When I told Bunney about this, he said, "Oh, well, he's biased. Ask the Chancellor." And the Chancellor, at that time, was Jack Peltason, a political scientist and economist, a guy that I respected. He said, "Well, I don't know much about content analysis, was the work scientific and valid?" I said, "It was." And he just simply said, "Publish it." But, I decided not to publish it right away, because about that time some psychiatrists in the American Psychiatric Association said something negative about Barry Goldwater without interviewing him. So, I waited till after the presidential election. Then I asked a colleague of mine in the school of business, to recommend a top rated non-psychiatric publication. He suggested Public Administration Review, published out of Washington, DC. He also said, "I think, they'll be glad, if it's a good paper, to publish it." The paper had a lot of statistics in it, but they published it. That was in 1988, I think. After it appeared, there were criticisms about "this psychiatric gobbledy goop"; this guy doesn't know what he's talking about. But, we know what happened to President Ronald Reagan; he developed Alzheimer's disease. I know that my cognitive impairment scales are very sensitive as well as valid. I kid about it sometimes, that it wouldn't be a bad idea to try it on the pilot of your airplane. It will even show whether somebody is on an antihistamine, alcohol, or benzodiazepine. It's very sensitive.

TB: Do you think content analysis can pick up early Alzheimer's better than other tests?

LG: Well, our speech analysis is very, very simple and easy to do. I noticed that recently, somebody got a test that picks up early Alzheimer's by giving people the name of 30 objects to remember. An ordinary person can remember 15, but an early Alzheimer's can only remember about seven or eight. My test will pick up an early Alzheimer at least as well.

TB: Was it also during the 1980s that you got involved with manganese and its possible contribution to violence?

LG: That was much later, probably in the 1990's.

TB: What about your research with PET? When did you do that?

LG: 1990's. It was unusual at that time for a single department of psychiatry to have a PET scan, but through the efforts of William Bunney and Monte Buchsbaum, we had one. It's very expensive but we got a cyclotron, and it almost drove us broke. Usually such instrumentation is under radiology.

TB: So you had a PET scan in the department and that is how you got involved?

LG: If you do a PET scan, you often have to combine it with MRI. So, I became involved in PET scan and MRI studies.

TB: Could you say something about the research you did with PET?

LG: Monte Buchsbaum was doing some research with PET in schizophrenia before he went to Mt. Sinai Medical School in New York. Dr. Bunney was also interested in doing studies with PET in schizophrenia. So I was involved in some of their research. But I had questions about the technique. As you know, when you do PET, you're measuring, not just the architecture of the brain and the skull, but you're measuring function, what's going on in the brain. People aren't saying anything because they're in the machine. But even if they are not saying anything that doesn't mean they're not thinking. So, how do you stop them from thinking because that might have an effect? Thinking about a love affair is different from thinking about being angry at a policeman. The conventional technique to control for that is to have the subjects engaged in pressing a button every time a light turns on. This procedure is supposed to block out random thoughts. I thought that this was a little bit naïve. So, I decided to do studies in which, instead of using this technique, we let the subject do nothing during the procedure, and then report verbally afterwards what they were thinking about while the PET scan was taken. With my technique, we were able to correlate findings in the PET scan with content analysis of language.

TB: Could you tell us what you actually did?

LG: Specifically, you give an injection of radioactive glucose and 20 minutes later, because it takes about twenty minutes to metabolize in the brain, you take a speech sample to learn what they were thinking about.

TB: What did you find?

LG: We found that the subject matter you are silently thinking about makes a difference in your cerebral glucose metabolic rates. Subjects were not told what to think about, but the level of anxiety and hostility showed up in significant differences in their PET scans. We published a paper

on our findings in *Comprehensive Psychiatry* with the title, “The effect of anxiety and hostility in silent mentation on cerebral glucose metabolism.” But then, I did studies to see whether the different kinds of anxiety or hostility in dreams would show up as differences in the parts of the brain involved.

TB: Did you find any differences?

LG: There are differences in PET scans when you are experiencing anxiety awake and when you are experiencing anxiety while dreaming. We published papers on our findings in *Brain Science* and other journals. That was the first time such papers were published. The brain is very complicated with regards to what part is involved with different emotions, and there is no other way we can study these matters, at this time, than the technique I used.

TB: What about the effects of other emotions?

LG: I got interested in studying the effects of hope and hopelessness on the PET scan. We used the same technique as we did with anxiety and hostility and we found differences. We published our findings of this research in the journal *Psychiatry*. I still have a paper that I think was ahead of its time. I scored normal individuals for social alienation and personal disorganization on the schizophrenia scales, and showed that the higher the scores, the more likely it is that parts of the left temporal lobe are involved. It’s interesting that some of the recent research on schizophrenia shows that in schizophrenia the left temporal lobe is involved. But it’s also involved in normal individuals, who are not schizophrenic; the greater their social alienation and the more disorganized they are, the higher their scores for glucose metabolic rates in the left temporal lobe.

TB: What you are showing is continuity between normal subjects and schizophrenics.

LG: That is right. Rather than, here’s a group of schizophrenics and here’s a group of nonschizophrenics and they’re altogether different with regards to brain functions, there is continuity. It may be, that if you do the statistics, you would get linear continuity rather than separate, discrete characteristics.

TB: You were tackling important theoretical issues in psychiatry using statistics.

LG: Statistics have got to be used, one way or the other. I feel that science has to be on a statistical basis for assertions to be valid; otherwise they are a matter of faith.

TB: Yes, but one must have or develop, as you did, a suitable instrument for the collection of relevant data to analyze with statistics. You developed a suitable instrument in your speech analysis to show that your assertions are valid.

LG: To prove it.

TB: What would you consider your most important contribution to psychopharmacology?

LG: That's like asking a guy with several children, which one do you like the best? I care about all of them. You're asking me to be objective. I think my contributions in the general field of neuropsychopharmacology are good and original. I think my contributions to the measurement of neurobiological and psychobiological states and to the computerized content of natural language or verbal texts are very important. I think the neurobiological studies with PET scan, or brain imaging, are important. I think, to me, they're all my children and they're equally important.

TB: I understand.

LG: I'm just telling how I feel about your question. You might think this guy is pretty narcissistic; he loves all his children, but I just think they're all relevant. And I'm not a good judge. Time, alone, will tell.

TB: Do you think that your content analysis of language should be used more extensively?

LG: I don't use the word, "should," because people would say this guy sounds like a controlling person. But I want to point out that the system can be applied to conversation. There were people that used our method to look at documents written before the French Revolution to see whether there was an increasing amount of hostility to the royalty of France in those years. You see, content analysis is getting more and more popular. It looks like it is much more sensitive than any other kind of psychiatric assessment. I'm having a growing conviction it's a very sensitive, useful measure, and in time, it might even be useful for the analysis of social issues.

TB: Am I correct that you are still active?

LG: Yes. I'm Professor Emeritus and working full time in the Department.

TB: What are you working on currently?

LG: I see patients, children and adults, maybe 15 to 20 hours a week. I do research and I'm writing papers. And I'm funded right now for a research project from NIDA.

TB: So, you still have an ongoing grant?

LG: I collaborate with one of the younger professors, Jerry McGuire, who is Director of Geriatrics and who has drug grants. So, we're getting verbal samples on some of those patients included in studies on grants for Alzheimer's drugs.

TB: What else are you doing on that research grant from NIDA?

LG: They have asked me to develop software that will detect and measure cognitive impairment in drug abusing patients.

TB: It seems that you have been involved in a wide range of activities. Is there any area we have not covered?

LG: In science?

TB: Any other activities you are involved with.

LG: I like to do art; but I'm an amateur artist. I do a little water-color painting and I have written a novel. I'm writing a documentary now on my personal experiences in World War II, when I was seeing thousands of neuropsychiatric cases. I've had a criticism of it from Simon Schuster. They think it's too academic, and I'm trying to rewrite it. I'm having fun with that. Now, is that going to be an important contribution? No, but I feel it is important to put on paper that neuropsychiatric casualties in war are usually de-emphasized and perceived as in conflict with patriotism. It seems all right to get a Purple Heart or honors in the military if you get injured. But neuropsychiatric casualties and how they affect people is suppressed. There are many men and women that served in the military who were traumatized. They didn't have a nervous breakdown, but it affected them, it scarred them, and it has long term adverse effects. It has affected their physical and mental health. Some of them die younger. So, I'm into that right now.

TB: That's the documentary you are rewriting.

LG: Yes, I'm trying to make a point. My book, *World War II Neuropsychiatric Casualties: Out of Sight, Out of Mind*, was published in 2004 by Nova Science Publishers, in New York. Its sales have been good.

TB: You are not only Professor of Psychiatry but also Professor of Social Science. Is there anything you would like to put on record about your activities in that area?

LG: I think that psychiatry is not just biological science, but it involves a person's behavior in society. I was active in the Social Science division of the University and, I think in retrospect, that I did a landmark study on the effect of sensory overload on behavior. I had a graduate student,

Daniel E. Bates, during that period of time, with a similar interest to mine. He and I built a dome like structure; I suppose ten feet in diameter at the bottom and put a subject in that dome-like structure lying down, looking upwards. We made a movie in Technicolor with strong music and odd colors and projected that onto the ceiling of the dome. We got verbal samples from our subjects before and after the sensory overload experience. There was no question that after being in that dome for fifteen minutes, they showed significant elevation on our schizophrenia scale. I published our findings, in 1973, together with John L. Haer and Daniel E. Bates with the title, "Effect of sensory overload on psychological state," in *Mental Health Digest*. There has been a lot of work done since that time in sensory gating, as that area of research is referred to now. There are some people in that situation who are able to compartmentalize events and perceptual experiences and shut things out, whereas others can't. We used the Rod and Frame tests, which indicate whether people are influenced by the frame in which the rod is placed or by surrounding events. We found that people who are influenced a lot by the surroundings are more susceptible to extrasensory overload. This research was done in the Social Science division, where I was working with graduate students. A lot of people have asked me since whether we still have that dome-like structure we built and the movie. I probably still have the movie. But these experiments are relevant to the concept of sensory gating. We did our research in normal subjects, but the research interest today is whether schizophrenics have insufficient gating and are overloaded by sensory experiences.

TB: You said there is lots of interest in sensory gating.

LG: There is a friend of mine, Prof. J. Christian Gillin in San Diego, who used some of our ideas in his studies in this area of research. I think there is something to this idea of gating impairment in schizophrenia.

TB: Is there any other research you did, or paper you published, that you would like to talk about?

LG: I already mentioned that I contributed a paper to a book entitled *What About Interrogation?* Usually, you and I don't get involved in interrogation. That's not our field. But I got involved, reviewed the literature on that subject and wrote a paper on it. I was asked by the military to do that. I suppose they were interested in what happens if our soldiers get captured by the Koreans in the war and put under torture. Dr. Jolly West, who was Department Chair of UCLA, was interested in the effects of interrogation, and what should one do in that situation.

TB: I heard of Jolly West's involvement in that area of research.

LG: After reviewing the literature I recommended taking LSD or something that makes you act crazy. They're not going to interrogate you; if they think you're crazy because they will believe your information is not reliable. As far as I know, my suggestions have been followed to some extent.

TB: Is there anything else we have not covered?

LG: We have done some studies on stuttering and found that risperidone reduces its severity. In the same paper, we also reported that stuttering does not interfere with IQ and stutterers might be brilliant in some areas but have a certain type of cognitive impairment. There are PET scan studies that support that.

TB: Was this your last paper so far?

LG: No, my last paper is on, "The detection of cognitive impairment from verbal samples." It is about that eventually doing our sampling test from voice recognition, using some of the new techniques and technology, so the speech wouldn't need to be typed. I would like to apply for a grant to do that.

TB: It would make it easier to do the test and would speed things up.

LG: Right.

TB: You are still active and moving ahead. Thank you for sharing all this information.

LG: It's been enjoyable talking to you.

TB: It was a pleasure listening to you.

LG: About one of my favorite subjects.

TB: Thank you.

26. JOHN F. GREDEN

TB: This is an interview with Dr. John Greden²⁸ for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College. It is December 2, 2002. I'm Thomas Ban. Could we begin with where you were born, your background, and how you decided to go into medicine?

JG: I'm John Greden and I'm honored to join the distinguished company of people interviewed for the historical archives. I was born in Rolling Stone, Minnesota. Jokingly, people give me a hard time about the fact that Rolling Stone was a very small town; when I grew up it had a population of 395 associates and me. I wasn't aware I might be going to medical school but it was probably by mother's influence. She was a registered nurse in a small community with no doctor; she was the person people called for medical advice, so I was exposed to this while growing up. Nevertheless, when I started college, I had plans to do something else because I was not even in a pre-medical curriculum. It was in my freshman year I decided to switch to medical school and that was one of the best decisions I ever made.

Whenever anybody asked, "What are you going to do," I replied, "I'm either going to be a psychiatrist or a surgeon." This was in the early 1960s, and when I would say that, people would reply, "Oh, be a surgeon." I was aware there was stigma associated with psychiatry. I got my undergraduate degree from the University of Minnesota and after I entered medical school, I found myself asking what I would like to do. Probably the most enjoyable course I had in my first year was neuroanatomy. After my first year, with a NIMH fellowship, I spent my summer vacation on a project interviewing depressed women and published on that project with my mentor. After I finished medical school, I did an internship at UCLA's Harbor General Hospital, in Los Angeles, California. It was one year after the Watts riots. At that time, my intention was to become a pediatrician. But, during the year at Harbor General, I found myself spending most of my free time reading about psychiatry. And, about two-thirds the way through the year, I decided to switch

²⁸ John F. Greden was born in Rolling Stone, Minnesota in 1942. He received his M.D. from the University of Minnesota in Minneapolis, Minnesota. After internship at the University of California at Los Angeles in California, he began a residency in psychiatry at the University of Minnesota, which he completed at Walter Reed Army Medical Center in Washington, D.C. during military service. He, then, joined the faculty of the Department of Psychiatry at the University of Michigan in Ann Arbor, Michigan. He was interviewed in San Juan, Puerto Rico on December 2, 2004.

from a pediatric residency to psychiatry. Again, that was one of the best decisions that I have ever made. Along the way I had married, Renee; we knew each other from our small community and intermittently dated since high school. So, I already had two small children by the time I had finished internship. There was turmoil because of Vietnam and I was in the last group of physicians subject to the draft under the Berry Plan. After one year of residency in psychiatry at the University of Minnesota, I was called to active duty, posted to Fort Sam Houston in Texas for basic training. From there, I ended up assigned to Fort Lee, Virginia, where I was what the army called a partially trained psychiatrist, looking after thirty thousand soldiers with another physician who had just completed psychiatric residency. It was great exposure to psychiatric problems and a wonderful opportunity to learn. We had to handle everything and were perceived as experts. To do the job, we had to read a lot and learn fast. Those were the years when the epidemic of drug abuse hit society at large and the military specifically. President Nixon considered it the number one public enemy and declared “war on drugs.” I ended up evaluating on the scope of the problem at Fort Lee and published my findings in the *Archives of General Psychiatry*. As time passed, I was becoming more and more interested in psychopharmacology.

TB: You mentioned you had one year of residency in Psychiatry at the University of Minnesota. Was Bert Schiele chairman of the department?

JG: The chair was Don Hastings. But Bert, a pioneer in psychopharmacology, was one of my mentors. Faruk Abuzzahab also taught us psychopharmacology. I did not think at the time that was the type of psychiatrist I would like to be; I was interested in a number disciplines and in integrating knowledge from them. I tend to call myself an integrator. I love neuroscience and I love to translate findings from neuroscience into clinical use. I also love the idea of moving forward; whatever project I do, I like to move forward with it.

TB: Where did you do your other years of residency and what did you do afterwards.

JG: I finished my residency at Walter Reed. After my residency, I was asked to stay on as associate director of research. But I also had an offer from the University of Michigan, and I chose to accept that appointment. I was still young and chose a colleague, Barney Carroll, who was the individual probably closest to what I wanted to do, as my mentor. Suddenly, I found myself learning more about neuroendocrinology and spent much of the next ten years trying to blend together my interest in the longitudinal course of depression in a Kraepelinian model, with my interest in

psychopharmacology and neuroendocrinology. We used the dexamethasone suppression test (DST) and I began to monitor what happens in the longitudinal course of depression with the hypothalamic-pituitary-adrenal axis. In collaboration with Barney Carroll, Michael Feinberg, Athanasios Zis, Roger Haskett, Ira Ball, and others, it was intriguing to find variables such as relapse, suicide, and others, were related to HPA dysregulation.

TB: Could you tell us about the DST?

JG: The DST was based on finding that administration of a small, 1 mg or 2 mg dose of dexamethasone, at night in normals shuts off hypothalamic-pituitary-adrenal secretion, as measured by suppression of the morning rise in plasma cortisol level; but 30% to 80% of depressed patients do not suppress this morning increase. The finding that cortisol “escapes” suppression is an indicator of the dysregulation of the hypothalamic-pituitary-adrenal axis in depression. People initially developed the wrong idea that DST might be just another useless laboratory test. Later it was recognized that the DST reflects what is going on in the brain of depressed patients. The hope that the DST might be the first laboratory test in psychiatry for deciding whether a depressive illness requires medication created a great deal of excitement in the United States.

TB: Did you participate in the development of the DST?

JG: I cannot take credit for that, but I was the first to use it in a longitudinal study.

TB: Didn't Barney Carroll start work with DST, while still in Australia?

JG: It was Barney who started it in Australia. From Australia, Barney went to Philadelphia, before he was recruited to the University of Michigan, a little bit before I arrived. With the approval of Al Silverman, the chair of the department, Barney and I converted 12 beds from a 24 bed inpatient service, into a clinical research unit for affective disorders. We called it the CSU, the Clinical Studies Unit for Affective Disorders, and also organized an outpatient clinic to follow patients who participated in protocols in the CSU. For ten years, it was like running a GCRC in Psychiatry. It was very productive and probably the most rewarding time in my life. In about 1983 or 1984, Dr. Carroll left and there was a short time, when we had turmoil in the department. I had taken a sabbatical, published several papers, and was promoted to Professor. I was still a young professor when people started asking me to become chairman of the department. I said, “No,” several times; I felt I already had the best job in the country, running the clinical studies unit. But the department started to fall apart, and in 1985, I was asked by the Dean to take over as acting chair. After

struggling for several months, I decided to accept. Otherwise, I might have ended up leaving Ann Arbor because of turmoil in the department. By then, we had three children and I loved Ann Arbor and the university. That was long time ago. I have been chairman for about eighteen years. In my early years, I set out to build a network for translational research. It was hard to pull things together and more and more I had to leave my specific laboratory responsibilities to pay attention to how to train a new generation of psychiatrists. I began to focus on trying to recruit young scholars and start people in research careers.

TB: What happened to your laboratory after you delegated some of your laboratory responsibilities?

JG: The laboratory has remained operational. It is in our Mental Health Research Institute (MHRI). The people we recruited were Huda Akil, a past president of this College and current president of the Society of Neurosciences, and Stan Watson, an internationally recognized neuroscientist. Elizabeth Young, a fellow of this College, is a product of our laboratory training. We all worked together but I was the engine of recruitment in those early years. Operations in the MHRI have continued but shifted from the traditional search for a laboratory test to molecular genetics, neuroimaging, and the study of proteomic mechanisms. Stan, Huda, Elizabeth, and a number of people who grew up in our department have remained. So the lab is very operational and has continued to be extremely productive in working on the basic science clinical interface.

TB: One of the former chairmen of your department, Al Silverman, was involved in research in psychophysiology. I remember him from the late 1950s or early 1960s. What happened to his laboratory?

JG: Al ran his lab, even as Chair, and I ended up inheriting part of the space, when I received a NIMH grant to study Psychomotor Regulation and Affective Disorders. I looked at facial electromyography and reactivated interest in the Omega Sign, a corrugator muscle activity seen in sadness. Now this research is done with fMRI, a far more sophisticated technique than EMG. I was also measuring speech periodicity by voice recordings and monitoring motility. The technologies were all rather primitive but we have come a long way since. But I inherited Dr. Silverman's lab space and used it for about five years. Right now, there is a great deal of emphasis in our department on sleep research. But the focus of activities, after Dr. Silverman's retirement, shifted from psychophysiology to stress and the neuroendocrine system, molecular

psychopharmacology, and neuroimaging. Now that I'm reflecting on it for the first time, it is an intriguing and exciting story. I didn't come prepared to go over this and find myself looking back and realizing there have been some very good things that emerged.

TB: You dedicated a considerable amount of your time as chairman to the development of research. Weren't you the chairman also of the faculty group practice at the University?

JG: In 1996, the sixteen clinical departments of the University of Michigan decided to form a faculty group practice. For whatever reason, I was elected the first Chair. When my elected term ended, I could have probably gone off to be a dean. I said, jokingly, to my wife Renee, "I wonder what I want to do when I grow up?" I should have been grown up by then, but apparently, I was still searching for what I wanted to do. I also had an opportunity to shift from academia to the pharmaceutical industry. Rather than become a dean or take a position with industry, I decided to take a sabbatical, and asked Dr. Schatzberg, another past president of this College and a very close friend, whether I could spend it in his department at Stanford. My idea was to pursue a different dream and, while on sabbatical, conceptualize a depression center. In February 1999, after I returned from sabbatical, I made a proposal to our school of administration to establish a comprehensive depression center. I envisaged a center that would incorporate inputs from many disciplines, not just from psychiatry. I thought we needed input from basic science, cognitive neuroscience, the social sciences, and expertise in epidemiology. By being there for all of those years, I knew a lot of research was going on in the different departments of our University. My idea was to bring all that expertise together. The idea might have been rather bold, but in December 2001, we got approval to establish the center, and in 2002, we also got approval for the construction of a new thirty-eight million dollar facility to house it. It will have fifty-eight thousand square feet, half for research. The Center has the largest representation from psychiatry and medicine, but also includes family medicine, obstetrics and gynecology, emergency medicine, geriatrics, cardiovascular medicine, and a cancer center. In all these areas, there are experts very interested in research on depression. The Center has input from the school of public health, social work, pharmacy, nursing, psychology, and biostatistics. By bringing all this expertise together, it serves as a research engine that produces a great deal of excitement. Last January, I spent my entire month preparing a proposal to NIH, requesting support to help build the research laboratories. It made it possible for us to expand our new facility beyond what I just described.

The fun part for me will be in constructing a new version of the clinical studies unit I had with Dr. Carroll twenty-five years ago, a model for the next generation. I'm very excited about what we can do. I believe we have laid a foundation in our field for future translational research by having an Institute that can move forward treatment, regardless whether it's with CRF antagonists, genetic therapies, or antagonizing neurotrophins. So, for the past five years, my challenge has been to wear this new hat.

TB: Over and above of all your other activities, you have been involved in mentoring several people.

JG: I have in the past fifteen years served as a mentor for about 14 Career Development Awardees.

TB: Could you name some of them?

JG: Well, some of the names I've already mentioned. I have been involved with Elizabeth Young's training, once our research fellow. Some of the others include Israel Liberzon, Bridget Tinden, and Helen Kales. There were also people, whose primary mentors were Stan Watson, Huda Akil, who I was mentoring in collaboration. We have an outstanding young scholar named Heather Flynn, interested to look at women who refuse to take medications because they are pregnant, and I decided to help mentor her.

TB: You have been very successful with your research teams.

JG: When I look back, I have a longing that it would have been nice to pursue more research of my own. But currently you need teams to make progress because of the vast array of knowledge required to pursue the work. It is necessary to bring people with different expertise together and that represents a challenge. You end up struggling to manage the teams and need administrative and interpersonal skills to keep people on the same page.

TB: You have also been active in the ACNP.

JG: I have been on the council now for several years and before that I was serving on the advocacy and the publications committee. I was also asked by the council to be a senior administrative editor and help to revise and restructure the college's publications. I was involved in the selection of the right people as editors for *The Fifth Generation of Progress*. We brought in Ken Davis, Dennis Charney, Joe Coyle, and Charlie Nemeroff to edit the book and Jim Edward Woodruff in doing the scientific web site of the ACNP Journal. I ended up having Bob Lenox in the role of journal editor. Now Charlie Nemeroff is doing it.

TB: When did you become a member of the ACNP?

JG: It was sometime in the 1970's. I became a Fellow about a decade ago.

TB: Would you like to comment on the annual meetings?

JG: The annual ACNP meetings have always been highlights for me. I remember when the teaching days started. The College has much to be proud of when it looks back on its past and membership.

TB: Let me switch to another topic. You have been wearing many hats successfully. How much of your time are you spending in clinical practice, seeing patients?

JG: I have continued to try to stay active clinically. For twenty-five years, I've had funding as a PI or Co-PI, and I've tried to have my clinical activity stay relevant to my ongoing clinical research grants. I have averaged about five to six hours of patient contact a week. In recent years, I see mostly VIP's. I am asked to do evaluations of people within our university or community. Some of these people I treat and follow subsequently. If I would not do that, I would lose the fine edge of my clinical skills. Five to six hours a week is probably not enough but I've tried to stay involved in clinical practice. As chairman of the department of psychiatry I'm responsible also for the MHRI. I have terrific leaders at the Institute. Stan Watson and Huda Akil, as codirectors, take care of the day-to-day activities. I am also the founder and executive director of the Michigan Depression Center I mentioned, and I guess it is taking about half my time. You made a nice compliment when you said, "I'm wearing a number of hats and I seem to be doing them successfully." I hadn't thought about it that way, because sometimes I worry I'm not doing any of them well. Still, there is one more activity I should add to the different activities we already talked about. I've become a bit of a "philanthropy development officer," as I call it. To make sure the depression center is a success, I set a goal to raise fifty million dollars to help in its' operations. At the time I set this goal, some of my colleagues at the University scoffed. But we have now been moving towards our target for about a year and a half and have raised about 19 1/2 million dollars already. So we are well on course. Many colleagues doubted people were going to donate for research in depression, but in actuality, many people are quite willing to do so. It's been very rewarding to see our region so responsive.

TB: You have been certainly very successful. Are you currently involved actively in any of the research projects at the Depression Center or the MHRI?

JG: I have continued to stay active and participate in our research. I'm the Co-PI on a grant we just submitted on the prevention of suicide that is focused on depression and alcohol use, the highest risk for suicide in our society. We have chosen to develop some programs as part of the depression center that looks at depression in college students, and I'm part of that project also. I have continued to play a role in the Star D project, although, the protocol in that project is followed by others.

TB: Do you have any special research interest these days?

JG: I've developed an interest in depression and pain, and especially in why is it that the SSRI's don't seem to work in patients with physical symptoms and pain; whereas, the old tricyclic antidepressants do. We might need to develop other strategies for these conditions, possibly using SNRIs. Many depressed patients are seen by primary care physicians. I believe that we must detect depression earlier, intervene earlier and more effectively to prevent its progression. That is a long-term interest of mine. To achieve this goal, we moved many of our people into family medicine, the cancer center, the cardiovascular center, the emergency room, and we are trying to work with people in those centers side by side, in a collaborative model, sharing expertise. Our colleagues at the University of Michigan have been wonderful. They love it. We have already learned people with depression who show up in family medicine and in the cancer center have a whole different array of symptoms than those who end up in psychiatric facilities.

TB: You mentioned that one of your current interests is in depression and pain.

JG: The pain story is like the other stories in depression. What you discover is that it's an orchestra and if something goes wrong you don't get good music. In addition to the endorphins and neurotrophins, traditional neurotransmitters, like norepinephrine and serotonin, play a role in sensitivity to pain. Among the pharmacological treatments, trazodone was considered to be especially useful, but many of the old tricyclic antidepressants, like imipramine, amitriptyline, and nortriptyline also have an effect on chronic pain associated with depression. When we moved into the era of the SSRI's, seeking for more selectivity, we tossed out anticholinergic side effects, and by doing that we have lost an effect that is relevant to depression. We've made great progress in the treatment of depression during the past decades, but we still have about thirty percent of the depressed population who don't respond at all, and probably, another thirty to forty percent, who respond only partially. From the total population, only thirty to forty percent achieve remission.

The group of non-responders or partial responders probably consists of individuals with an alteration in a circuit other than those targeted by selective re-uptake blockers. These are people with lots of physical symptoms, who have pain and are chronically ill. Our challenge is to move into a new era in which we pay more attention to getting people better and keeping them well than to having more and more selective drugs with fewer and fewer side effects. We need to focus on depression associated with physical symptoms. I doubt it, but it's not impossible we need to go back to the tricyclic antidepressants and trazodone. For this population the right medication might be dual or triple reuptake inhibitors or an entirely different group of drugs.

TB: You mentioned that we might have lost something by trying to eliminate the anticholinergic effects of antidepressants. Could you say something about the possible role of the cholinergic system in depression and antidepressant effects?

JG: I became interested in the cholinergic system while working with Dr. Carroll, because of its' apparent role in pushing the HPA axis, probably by being involved in the release of CRH. At one point in time, we were trying to address this by looking at the effects of physostigmine infusions. We became interested in what happens to people when they suddenly discontinue their tricyclic antidepressants, and we were first to describe what we called a "cholinergic supersensitivity pattern" that consists of nausea, nightmares, sleep disturbances and recurrence of depressive symptoms. We also discovered re-instituting the antidepressant with anticholinergic effects would suddenly alleviate the syndrome. I wasn't surprised when I learned there is also a withdrawal syndrome to SSRIs that is different from the withdrawal syndrome with tricyclic antidepressants. I was, frankly, a strong supporter of the SSRIs when they were introduced because I saw many people with blurred vision and dry mouth on the old drugs. I had to get people to suck grapes or other things to keep them on their medications. But now it's clear to me that if we pursue developing more and more selective drugs we block scientific development. To move forward we probably need to pick up some combinations, and I hope our colleagues in industry will help us do that.

TB: Are you involved in research with any of the newer drugs?

JG: We are involved with some in our depression center. I'm very much interested in the SNRI story and following closely the research with duloxetine, milnacipran, and venlafaxine. Not long ago, I completed the chapter on duloxetine and milnacipran for a psychopharmacology textbook

edited by Drs. Schatzberg and Nemeroff. The molecular structure of these drugs and their mechanism of action is currently in the focus of my interest, as I said, I am more of an integrator. With the exception of longitudinal monitoring of depression and trying to work out ways to get depressed patients better and keep them well, I never stayed with any research project over an extended period. My latest area of interest is in minimally invasive brain stimulation strategies, regardless whether it is with repeated transcranial magnetic stimulation, rTMS, vagal nerve stimulation, VNS, or deep brain stimulation. We have started to move into this area of research. I doubt we will have one magic silver bullet that will hit all depressions because I think we have different pathophysiologies.

TB: We have only a few more minutes left and I'm wondering whether you could say something about your publications?

JG: My first publication that attracted attention was related to caffeine. I could have chosen to pursue that as an entire field, and it would have been fun. If you coin a syndrome like caffeinism as I did, you can be proud. I was member of the team in a series of publications on neuroendocrine strategies, but the paper I'm proudest of is the one on, "Serial Neuroendocrine Monitoring, Normalization of the DST, a Laboratory Indicator of Improvement," published in *Biological Psychiatry*. Most people who read it get the point I was trying to make, namely that the DST reflects what's happening in the brain, and it's not just clinical features and phenomenology one should pay attention to. To address the phenomenological and genetic heterogeneity of depressive illness as related to treatment response, we would need to deal with the heterogeneity of transporters. My 5-HT transporter polymorphism may be totally different than yours; and if we're both given the same drug, what are the odds both of us will respond in the same way. It's the same with the norepinephrine transporter, the dopamine transporter, and with a number of other polymorphisms. That'll be a new exciting era to work in. I hope I will be part of that and make some contribution to it. So far, much of the excitement about the gains we've made in understanding depressive illness has been accompanied by frustration. I don't think we're targeting brand new treatments in the right way and that represents a challenge.

TB: So you would like to see novel ways for targeting brand new treatments and using genetic technology for prediction of responsiveness to them.

JG: Very much so.

TB: Anything else you would like to see to happen?

JG: One of my dreams, a comprehensive depression center, has already become a reality. It was also my privilege to testify before the White House Freedom Commission about the state of affairs of our mental health delivery system; I basically said, "Depression must be a key part of this." According to the World Health Organization, depressive illnesses are the leading cause of disability in the world, and if we are not making progress in the number one disease among the one hundred most important diseases, we need a different strategy. This was partially why I pushed for the establishment of our depression center and advocated we should develop a national network of depression centers. That's my current passion. Unless we bring clinical expertise, basic science expertise, and social sciences into the field, we're not going to make the difference we seek. All we know now is, if someone has a depressive illness with a constellation of symptoms, we give an antidepressant and, if it does not work after eight weeks, we try another one. I believe science should enable us to be more specific. TB: If the integration of different disciplines is done properly?

JG: The integration of contributions from different disciplines is the challenge; to bring things together optimally.

TB: On this note, we conclude this interview with Dr Greden. Thank you for sharing this information with us.

JG: Thank you. I remember when this oral history project started; I thought it was for senior people. So, when I was contacted to participate, I thought, does that mean I'm there?

27. KATHERINE A. HALMI

TB: We are at the Annual Meeting of the American College of Neuropsychopharmacology in Waikoloa, Hawaii. It is December 10, 2001, and we are going to do an interview for the Archives of the College with Dr. Katherine Halmi.²⁹ It is December 10, 2001. I am Thomas Ban.

Let us start from the very beginning. When and where were you born? If you could tell us something about your early interests, education and how you got into the area of eating disorders.

KH: I was born on October 23, 1939. Most women don't like to give the date when they were born, but I'm over that at this point in my life. There is something satisfying to admitting I am the grandmother of the eating disorder field. I was born in St. Paul, Minnesota and from there, I received my education in the Midwest with a General Motor's scholarship to the University of Iowa for my B.A. and M.D. degrees. My medical interests were in endocrinology. I initially completed pediatric training and began working with Professor Zellweger, who was one of the first pediatricians to do genetic research. When I was a medical student, I learned how to do chromosome counts in Professor Zellweger's laboratory, and that was my spur to interest in research.

TB: So, Dr. Zellweger had an important impact on your life?

KH: Dr. Zellweger had an important influence in developing my research interest. Then, I was coached by my first husband, Nicholas Halmi, a well-known basic endocrine researcher and the editor of *Endocrinology*. He taught me how to think very precisely and how to respect scientific quality. I think that is a very important thing in developing your research career. He was a severe critic, in the best Hungarian-Jewish tradition. So, I quickly learned how to think clearly and defend myself.

TB: Where did you move from Iowa?

KH: I became board certified in pediatrics and joined the faculty at the University of Iowa, studying cortisol metabolism.

TB: Was this your first research project?

²⁹ Katherine Halmi was born in St. Paul, Minnesota in 1939. She received her M.D. degree and completed pediatrics training at the University of Iowa. She was interviewed in Waikoloa, Hawaii on December 10, 2001.

KH: My initial research was with Dr. Zellweger.

TB: When did you have your first publication and what was it on?

KH: My first publication was on identifying Trisomy 18 in Dr. Zellweger's lab.

TB: When was that?

KH: In 1968.

TB: It was your first publication and your first research project?

KH: Right.

TB: And you were a resident at the time?

KH: I was a pediatric resident, in the process of completing my residency. I became more and more interested in behavior and did a fellowship in child development. From there, I decided I was ignorant in understanding behavior and went into psychiatry.

TB: So, you moved from pediatrics to psychiatry in the early 1970's?

KH: Right. At that time, George Winokur became the Chairman of the Iowa Department of Psychiatry. He was just a wonderful supporter of research and an excellent investigator himself. That was a good opportunity and he taught me the methodology and principles of clinical research. He also provided the environment, opportunity and time to do the research.

TB: After your residency in pediatrics you did a residency in psychiatry?

KH: I completed a residency in both. When I was a psychiatric resident, I got into eating disorders. Dr. Winokur came to me one day and said, "I have this young lady on the unit that I believe has anorexia nervosa. I want you to investigate and take care of her. There are very few publications on anorexia and nobody knows much about it, so I would like you to look into it." I carefully went over the literature and he was right. There were very few publications. I examined the young lady carefully and decided she did not have anorexia nervosa. She really suffered from schizophrenia because her delusion was that different colors of food would erode her gut. That is not the kind of delusion present in anorexia nervosa. The problem patients with anorexia have is denial of their illness and the refusal to recognize that starvation may cause death. It is not the same quality as a psychotic delusion. Having learned how to argue aggressively in my training, I presented that to Dr. Winokur. To his credit, he acknowledged it. Then he went on to say that the University of Iowa Psychopathic Hospital had an unusual collection of records because it was one of the four original psychopathic hospitals. They had a wonderful record system, which Dr. Winokur was

using for his schizophrenia studies. Starting when I was a first year psychiatry resident, I spent every lunch hour down in the medical records room. After I devised various criteria, I went through about 3,000 records. Nobody had classified anorexia nervosa in those days, and it was often coded as a psychophysiological gastrointestinal disturbance. Among the almost 3,000 records, I was able to find 96 young women and 4 men who met the Feighner criteria for anorexia.

TB: Was this before or after 1974?

KH: This was before.

TB: About the time the Feighner criteria was published, in 1972?

KH: Yes. My first publication in the field of eating disorders was in the *Journal of Psychosomatic Medicine* on the group of patients from the chart research. Then, I decided to follow them up and was able to locate 79 patients, which was fairly good for record research. I admitted them to the clinical research center and conducted a series of endocrine investigations and standardized interviews. That resulted in a longitudinal follow up publication and propelled me into becoming more interested in eating disorders.

TB: You read through those famous records. Can you tell us how they were structured?

KH: The ones at the psychopathic hospital were structured, but those in the medical school were not. I had to go through many records in internal medicine, as well, because people were not identified as having a psychiatric illness at that time. Those in the psychiatric hospital had very long descriptions of family history and of the patient's personal development as a child. It was excellent descriptive writing, which we often don't see today. That was an invaluable collection. From that, I went to my Chairman, who was eager to support me, and who now stated I was an expert in the treatment of eating disorders, which of course, I wasn't. Nevertheless, I soon began receiving referrals because Dr. Winokur announced my expertise to the State Psychiatric Association. So, I had to quickly set up a program. That is how medicine was practiced in those days. At that time, the only book on anorexia nervosa was by Bliss and Branch, which emphasized their hypothesis that a hypothalamic disturbance was present with deficient pituitary secretion of follicle stimulating hormone (FSH), luteinizing hormone (LH), and so forth. But they didn't have any recommendation for treatment. Then, there was a group from London, England, Professors Russell and Crisp, who were using gross behavior methods at the time, putting people in bed until they reached their target weight. Since those early days, cognitive behavioral therapy has

developed and is much more sophisticated. Along with that, psychopharmacology evolved. Many patients were treated with chlorpromazine, which reduced their exercising, as well as ruminations about food and being thin. It was exceedingly helpful, but there has never been a double blind, randomly assigned, controlled study with chlorpromazine. In the European, especially the German literature, there are many cumulative case reports in anorexia nervosa treated with the drug, but no one has ever done a double blind study. We wanted to do that, but it was impossible to get funding. As a pediatrician, I used chlorpromazine with effective results in agitated patients. I still use it in many cases for severely emaciated patients, starting with 10 mg half an hour before meals in liquid form, then, gradually increasing the dose while monitoring lying and standing blood pressure. In studying the medication management of anorexia nervosa, we have a huge problem because it is almost impossible to complete an adequate sample.

TB: So, you had problems in recruiting patients?

KH: Right.

TB: Did you work at a clinic?

KH: Well, I developed my own clinic.

TB: Did you have an eating disorder clinic?

KH: You have to remember, the population of Iowa City was only 40,000 and it probably still is. We had a very good socialized medicine system, whereby cars went out from the University of Iowa Medical Center all over the state, bringing in medically ill patients. An outpatient clinic wasn't feasible, so I had an inpatient operation in the clinical research center. I needed to establish my independence in treating these people the way I wanted and avoid the administrative structure of the psychopathic hospital. So, I developed research protocols and every patient was on one or the other. It was fortunate for me that the clinical research center needed to have their beds filled, so I could work out a contract with them.

TB: Where did your patients come from?

KH: From the entire state of Iowa, because the state cars would bring them in. As I began publishing and became known in the field, I would get them from out of state, as well.

TB: Am I correct that most of your patients had anorexia nervosa?

KH: Predominantly. Bulimia nervosa was not really recognized as a separate entity until about 1979. All of us doing research in the area recognized the clinical and even physiological

differences that existed between the anorexia nervosa restricting patient and the anorexia nervosa binge-purge patient. My studies were some of the first to differentiate these. The binge-purge patient has much higher co-morbidity with alcohol abuse, drug abuse, and Axis II personality disturbances, especially cluster B, the impulsive type. They also have differences in response to serotonergic challenge tests. Those who binge and purge have a decreased response of prolactin to fenfluramine challenge; whereas the restrictors, if they are not severely emaciated, have little diminished response. We began to differentiate the subtypes, but then Russell identified a group of patients who had normal weight and were bingeing and vomiting. Once a group of patients has been identified, people start finding the cases. That happened all over our country. Cases were publicized and bulimia nervosa became an independent diagnosis.

TB: So, physiological differences in patients were associated with differences in pharmacological responsiveness?

KH: That was determined later, but in the 1970's, there were several different approaches. One was the development of cognitive behavioral therapy, and Stewart Agras at Stanford University was highly instrumental in that. Stewart was one of the first, along with me later, to develop controlled treatment studies, examining the efficacy of various medications and cognitive behavior therapy in treating anorexia first, and then bulimia. Agras developed some more sophisticated forms of cognitive behavior therapy (CBT). Professor Russell in London had done mainly endocrine research, while Crisp, also in London, had a very psychodynamic approach, even though he also used strong behavioral contingencies and chlorpromazine. In the United States, at that time, there wasn't any eating disorder controlled treatment research other than Agras, myself, and collaborators. There were psychoanalysts, Hilda Bruch and Minuchin, who developed a family therapy for anorexia nervosa. The first international meeting was at the National Institute of Mental Health, sponsored by Vigersky who was an endocrinologist. At that meeting, a small group of eating disorder experts included Stewart Agras, Hilda Bruch, Crisp, Russell, and me. Then, there were some invited people that sat around on the outside. The meeting was especially amusing because Crisp and Russell did not believe Minuchin's exaggerated results that family therapy cured these patients, and they questioned him intensively. He got very angry, banged his fist on the table, and walked out.

TB: Did he come back?

KH: No, he did not. But, one has to give him credit for developing and emphasizing family therapy. This led to a series of studies that developed, predominantly in London, examining what type of family therapy and for whom it was effective. Today, there are controlled studies to show that family counseling of some sort is essential for children under the age of 18.

TB: When did this first meeting take place?

KH: In 1976.

TB: Did people working in the field come from all around the world?

KH: Right. At that meeting, much attention was paid to endocrine research. I did some of those early studies at the University of Iowa.

TB: What proportion of the participants were psychiatrists and what proportion endocrinologists?

KH: I would say only about a quarter were endocrinologists and the others psychiatrists.

TB: So, the meeting was held before some of the pharmacological research was done with bulimia nervosa?

KH: Yes. Since then, many controlled pharmacological studies have been conducted for bulimia nervosa, because our challenge tests indicated that there was a definite deficiency of serotonin regulation in normal weight bulimia nervosa patients.

TB: When did the challenge tests come about?

KH: They came about in the 1980's. Those were done with m-chlorophenylpiperazine (MCP) and, then, of course, serotonin turnover was studied with CSF samples at the NIH by Walter Kaye. Since the 1980's, Walter Kaye has been a pre-eminent researcher, both in the endocrinology and neuroendocrinology of eating disorders.

TB: When, were the biochemical studies on CSF, conducted?

KH: In the 1980's. That was also developed with Walter Kaye at the National Institute of Health. Because it is so difficult to get patients with anorexia nervosa to cooperate, the area is riddled with the problem of adequate sample size. Most of Walter Kaye's CSF studies have never been replicated because we cannot get enough patients. What is unique about those studies is that he was able to get continuity of patients when they were acutely ill and after weight restoration.

TB: When did you move from Iowa to New York?

KH: In 1979.

TB: What was the status of your studies when you moved?

KH: I had already completed the first multicenter study examining the efficacy of cyproheptadine and cognitive behavioral therapy in anorexia nervosa. That was my first NIH grant. It was actually a multi-site treatment grant.

TB: How many other sites?

KH: There was the University of Minnesota and the Illinois State Psychiatric Institute. We were interested in cyproheptadine because it was a serotonergic antagonist, and serotonin produces fullness and satiety. We thought if we could decrease the action of serotonin, it might facilitate weight gain in patients with anorexia. It turned out this hypothesis was probably wrong because anorectics are hungry unless they are extremely emaciated. The reason why serotonin facilitated weight gain to a very modest degree was probably due to its antihistaminic effects. We then placed activity monitors on patients' wrists and ankles and were able to show that high doses of cyproheptadine, up to 24 mg a day, significantly reduced physical activity. That was probably the mechanism whereby they were gaining weight and why it was so modest.

TB: In how many centers was the research conducted?

KH: We had three centers.

TB: In Chicago, Minnesota, and Iowa City?

KH: Right, for the treatment study. The activity study was at Cornell, after I moved.

TB: How many patients did you have, altogether?

KH: In the treatment study, about 96 patients.

TB: That was quite a good sample size.

KH: It was a very good sample size.

TB: You had cognitive therapy in that study?

KH: The cognitive therapy was a strong behavioral component. We learned it was very difficult to study CB in anorexia nervosa inpatients. Back when we didn't have managed care, it was possible to treat them in an inpatient setting until they got to their target weight. We learned another important principle; you can't randomly assign anorexia nervosa patients, who are near death, to a therapy. We had several other problems. The nursing staff became convinced that cognitive behavioral therapy was absolutely essential because it helped them in managing the patients. Behind our backs, they were instituting various cognitive behavioral principles

surreptitiously. So, when we analyzed the data, there was no statistical difference between cyproheptadine and cognitive behavioral therapy, since all the patients were indirectly receiving CBT. You can't compare psychotherapy with another treatment on the same unit.

TB: Where did you publish the findings?

KH: That was published in the *British Journal of Psychiatry*. It was in a series of five publications in that journal.

TB: What year?

KH: In 1979.

TB: Was your study the first in a series of multi-center studies in that area of research?

KH: It was the very first multi-center study in the treatment of eating disorders, examining the efficacy of a pharmacological treatment by comparing cyproheptadine with cognitive behavior therapy.

TB: Didn't you carry out some research with chlorpromazine?

KH: Not systematically, because I was never able to get that funded, which shows that the whims of research committees sometimes dictate the direction of research.

TB: Did you work with any of the other neuroleptics?

KH: I used only chlorpromazine and cyproheptadine. With bulimia nervosa, it soon became evident that any antidepressant was effective in reducing binge-purge behavior. Bulimics are very willing to participate in trials; they are motivated to get over their illness, and thus, there are about 40 controlled, randomly assigned antidepressant-placebo trials for bulimia nervosa worldwide.

TB: So they are very different, in that respect, from the patients with anorexia nervosa. Are patients with bulimia very anxious?

KH: They are anxious to get over their illness. That is a huge difference. So, we became involved in those studies, which initially included the tricyclic antidepressants and the SSRI's, when they are available.

TB: Which ones?

KH: Everything was studied. All antidepressant medications, irrespective of structure had about the same efficacy. Only 20 to 30% of patients had a complete cessation of bingeing and vomiting and about 40% had a 50% reduction. The drugs produce some relief but aren't curative. We are still at that stage today, but we have also done studies with cognitive behavioral therapy and

comparison studies with medications. Today, cognitive behavioral therapy, which is now highly sophisticated with organized special treatment manuals, is the state of the art treatment. It results in about 40-50% complete cessation of bingeing and vomiting with about 70% of the patients reducing their bingeing and purging by 50%.

TB: Was this research done already in New York?

KH: Right.

TB: It was in your new setting. In Iowa, you had an eating disorder unit. By the way, was your eating disorder unit in Iowa the first eating disorder unit in the country?

KH: Not specifically, because it was in the context of the clinical research center in internal medicine. There were other units in those years being set up, but nothing was exclusively eating disorders. Arnie Anderson at John Hopkins set up an eating disorder unit; the NIMH did, and so, they were beginning to develop. The problem was that I couldn't forever depend on the clinical research center. I had this wonderful opportunity at Cornell Medical College in the Westchester division, which had a 300 bed psychiatric hospital, known in the past as Bloomingdale's, to have a 20 bed unit and run my own operation with the independence I needed. Then, I moved to New York. It was easier getting patients because of the huge Metropolitan population.

TB: Did you have a free hand in setting things up in New York as you wished?

KH: Pretty much so. The thing that was missing there was lack of proximity to the main hospital. It was 35 miles away. That was a drawback.

TB: You had grants to carry out your first studies of cognitive therapy and cyproheptadine.

Were you able to get funding in New York?

KH: I have had funding my entire career. When I got to New York, I also obtained a grant to study the comparison of amitriptyline and cyproheptadine in treating anorexia nervosa. That was a collaborative study with the University of Minnesota. We completed that and then I had a grant to do a longitudinal follow-up.

TB: What did you find?

KH: We found that neither drug was dramatically effective in increasing weight gain. Both were equally effective, but to a modest degree, in reducing the length of time for patients to get to their target weight. The average time was 14 days. There were far fewer side effects with cyproheptadine than with amitriptyline.

TB: Fewer anticholinergic effects?

KH: Yes. Cyproheptadine was effective in causing weight gain exclusively in the anorectic restricting types and not in the anorectic bulimia types. This was exciting information that made good sense in terms of what we were finding in our physiological studies because the bulimics had a deficiency of serotonin, whereas the restricting anorectics did not, unless they were severely emaciated. That went along nicely with the studies Walter Kaye was conducting at the National Institute of Health. He was very excited about our treatment findings because his CSF studies showed that the bulimia nervosa patients had a significantly decreased serotonin turnover, compared with the restricting type. So, we, essentially, had information from two different types of studies to indicate that the serotonin dysregulation occurred in both subtypes, but to a different degree. Then, I conducted, with the University of Minnesota, a long term follow-up study on those original patients we treated in Iowa, including endocrine studies.

TB: On how many of the patients could you get follow up information?

KH: We actually got follow up information on 100% of this set from Iowa; and Minnesota and Chicago were not part of the study. This was published in the *Archives of General Psychiatry*. Our follow-up studies had rather grim results. At the 10 year follow-up, 7% had died; only a fourth of them were completely cured; and about a fourth of them were still very chronically ill. The other 50% were in various stages of illness. That brought to light that anorexia, in a very systemically studied follow-up, is a serious and chronic disorder. That study has been the most complete follow-up with a large sample size that has ever been conducted. One of the reasons for the 100% follow-up, was that many of those patients were from the Midwest, where people tend not to move as frequently, compared to New York. They also tend to be more compliant with follow up in treatment protocols and studies. In New York, people are very mobile; they are far less cooperative, and it is a much greater challenge to do any kind of study, even though you have a huge population base.

TB: Was your first study in New York the cyproheptadine and amitriptyline comparison?

KH: That is right.

TB: What did you do after that study?

KH: Well, we conducted the follow up study from New York, because we had funding to set up an office back in Iowa City, and I had a research assistant, who moved there, and flew all over the country.

TB: Did you do any other research at the time?

KH: I became involved in pharmacological treatment studies with bulimia nervosa using the serotonin reuptake inhibitors.

TB: Was this research done in the mid '80's?

KH: Yes, and then, I did some work with Peter Stokes on endocrine studies and anorexia. Previously, at Iowa and New York, we found that the deficiency of LH and FSH was not a pituitary deficiency, but rather a deficiency of the hypothalamic secretion of gonadotropin releasing hormone. We did a study injecting luteinizing hormone-releasing hormone (LHRH) into anorectic patients and found that their response was adequate, even though they were emaciated. So it stimulated the pituitary to release these hormones. That was published in the *Archives of General Psychiatry*. The results surprised us. We didn't think it was going to be that effective, but it definitely proved that the problem of amenorrhea was at the hypothalamic level and that it was not producing gonadotropin releasing hormone. Then Stokes and I were interested in examining the function of the dopaminergic system. We did challenge tests with apomorphine and chlorpromazine, measuring prolactin response. In that study, we were able to show that there was a probable defect at the dopamine postsynaptic receptor in anorexia nervosa patients. The reason we came to that conclusion was that our studies showed the deficiency when these patients were emaciated and after weight recovery. It has become so fashionable to just focus on the serotonergic system that it is difficult to get funding to study the dopaminergic system. Now, I am involved in a five nation study on the genetics of these patients and we are getting some exciting preliminary findings to indicate that the dopaminergic system is also involved significantly in anorexia nervosa.

TB: Isn't the dopaminergic system involved in self-stimulating behavior?

KH: Animal studies show dopamine function is complex because in the paraventricular nucleus it has different functions, depending on the stimulation. Low amounts can stimulate appetite and high amounts can definitely decrease it. So it has a complex function. What was so appealing about serotonin was it was less complex. If you destroy the serotonergic pathways in the

paraventricular nucleus, the animal has no satiety and will eat and become obese. Most of the hypotheses concerning dopamine are reward reinforcement hypotheses. Bulimia, especially the binge and purging behavior, has characteristics in common with addictive behaviors. We use many of the same cognitive behavioral principles also used in treating addictive disorders, because bulimia nervosa has a high reinforcing aspect to it. We know that animals will reinforce the dopaminergic system for food.

TB: The dopamine system seems to be involved in both increasing and decreasing eating behavior.

KH: Avoidance of eating in anorexia alleviates anxiety in patients and can be a self-stimulating behavior. They become very anxious if they have to eat, because that means gaining weight. If you are a normal weight healthy person, you have to face the responsibilities of an adult person. That is the core psychological dynamic. Anorectic patients do not want to face the responsibilities of interpersonal relationships in dealing with their environment. Maintaining the illness is a strong secondary reinforcement. They are absolutely terrified to give up their illness and totally unmotivated to enter treatment. No anorectic wants to be treated, because abstinence from eating provides a reward.

TB: You mentioned a five centers multinational study. Which are the five countries?

KH: This is a study that began about almost 10 years ago, funded by the Price Foundation.

TB: Did it start in the early 1990s?

KH: Right. Walter Kaye in Pittsburgh is the overall organizer, but it involves Wade Berrittini, whose laboratory is responsible for doing the genetic linkage analyses and a group from the NIH that began the research for dopamine and serotonin polymorphisms. It also involves UCLA, my center at Cornell, the University of Pittsburgh, a private clinic associated with the University of Munich in Germany, and the University of Toronto. Originally, it involved a center in London that is no longer involved.

TB: So, in some of the countries there are several centers?

KH: There also was a center in Italy for the original pilot investigation. Now the study involves only Germany and Canada. We have added some other areas that can collect patients in the United States, but not university centers.

TB: What is the size of the study population?

KH: The Price Foundation sample size is very large. We probably have a unique and precious sample, something like 100 anorexia nervosa sibling pairs in two categories, anorexia nervosa restricting type with a sibling who has the same disorder and anorexia nervosa restricting proband with an anorectic-bulimic sibling. I can't remember the exact numbers of those two types, but I believe we have 104 sibling pairs. In our bulimia study, there are well over 200 sibling pairs. We have blood for DNA on all these patients and a very thorough systematic interview. This includes the Structured Clinical Interview for DSM diagnoses (SCIDS), measuring personality traits with the Temperament and Character Inventory (TCI), depression with Hamilton ratings, and other specific eating disorder psychopathological characteristics with validated instruments. All of our interviewers and raters have established an acceptable K score. It is a very special sample.

TB: Can you say something about the findings?

KH: I am under pressure not to reveal these until they are published.

TB: That is fine.

KH: What I am allowed to say is that there is strong linkage on Chromosome I for the anorexia nervosa restricting type. This area of Chromosome I is interesting because it also involves a significant serotonin receptor site and an opioid receptor site, both of which we are interested in. All these papers have been submitted for publication. So that's what I am allowed to say at this time.

TB: Thank you for this information.

KH: This is the direction of research for anorexia nervosa, at this time. It means probably another 10-20 years of very painstaking research, because once you identify a cluster of genes, you have to determine what proteins they produce and what the proteins do. That is the way to go, because every time a new peptide has been identified, like orexin that affects the appetite, everybody jumps on the bandwagon to measure it in anorectic patients. They think this is going to be the cure for anorexia nervosa, developing antagonists or an agonist to the peptide. That is simply not where it lies. This disorder is very complex. There are going to be multiple factors that contribute to the biological vulnerability. It is not going to be one single peptide.

TB: Is there any other research project you would like to mention?

KH: We continue to try to refine treatment techniques. With the issue of managed care and the unavailability of good, well-trained therapists in state of the art treatment, I am in the process of

doing a cost effectiveness study. This examines both efficacy and efficiency in a collaborative study with the Universities of Stanford, Minnesota, and North Dakota, four centers in which we are examining cost effectiveness and treatment efficacy in two arms of treatment for bulimia nervosa. Over the years, bulimia nervosa has been identified and has become far more prevalent than anorexia. About 3% of women in America will have bulimia nervosa at some time in their life. So, one arm of treatment starts out with a guided self-help manual, which is based on the principles of cognitive behavioral therapy. An untrained social worker can read the manual and guide the patient through it, seeing her briefly once a week for 8-10 sessions. If, at the end of that period, the patient hasn't reduced her bingeing and vomiting, she will be assigned fluoxetine, which has been proven to have some effect. That is less costly than state of the art psychotherapy. She is evaluated after eight weeks, and if she is not responding, she will begin CBT. In previous studies we have done with Stanford, we were able to predict after only six sessions of CBT what the outcome would be for the standard course of 20 treatment sessions. Because of this finding, in our new grant, we analyze every patient after six sessions, and if they haven't reduced their bingeing and purging by 70%, we begin fluoxetine. We carry on the CBT for the full 20 sessions, along with fluoxetine. We are following all these patients for a year. It has been wonderful collaborating with Helena Kramer, because she has been able to use signal detection analyses, which allow us to identify and predict what set of patient variables predict outcome.

TB: Could you elaborate on signal detection?

KH: It is a complex analysis taking all sorts of variables every week during the course of treatment and assessing where the patient is at that point in time.

TB: You said that you are using fluoxetine because there is some evidence of efficacy?

KH: Right.

TB: What about other SSRI's? Are they used?

KH: Efficacy of fluoxetine has been shown in a double blind controlled study for reducing binge-purge behavior. In my clinic and on the inpatient unit, we use other SSRI's and so does everybody in private practice. Other pharmaceutical companies have been riding the coattails of the company who did the first study because the mechanisms of these drugs are very similar. In clinical practice, for example, if we want more anti-anxiety or sedating effect, we use paroxetine; although, there has been no double blind controlled study.

TB: So, efficacy has only been demonstrated with fluoxetine.

KH: Right.

TB: Is there any comparative study of a tricyclic and fluoxetine?

KH: No, there is not. Tricyclics aren't used because of the side effects. There are patients who do not respond well to fluoxetine and, for those, we use desipramine. There have been a couple of studies, including ours, in which we added desipramine after fluoxetine and the response was not impressive.

TB: Was this done on the basis of theoretical considerations?

KH: Yes.

TB: Because desipramine is more selective for norepinephrine?

KH: Right. Bulimia nervosa patients have high co-morbidities with depression and anxiety disorders. Some patients who have severe depression concurrent with a lot of anxiety don't respond to SSRI's. We may also use venlafaxine because that affects the norepinephrine reuptake system as well, and some patients respond to that.

TB: What doses are you using for anorexia?

KH: The same doses one uses for depression. We only use venlafaxine after SSRI's have failed. The problem is if you increase the dose very much, then you start getting the anticholinergic side effects.

TB: So, the primary treatment has remained cognitive behavior therapy?

KH: In bulimia. In anorexia, after the atypical antipsychotics came out, I now use olanzapine instead of chlorpromazine for patients who are extremely emaciated. Many anorectic patients have read about how that drug induces weight gain. I have to promise I will stop the medication as soon as they get close to their target weight.

TB: Are they very concerned and reluctant to take the medication?

KH: That is right, but with olanzapine, there are just case reports and no published double blind study.

TB: Am I correct, that none of the antipsychotics were studied properly, as yet, in this group of patients?

KH: Way back in the early 1980's, there was a small study with pimozide and one of the other antipsychotics, and it didn't show dramatic effects.

TB: Was pimozide chosen because of its selectiveness for dopaminergic structures?

KH: Yes.

TB: So, it had some effects?

KH: It had a very modest effect.

TB: Is pimozide available today in the U.S.?

KH: It is, but we don't use it because it is not very effective. We use olanzapine or chlorpromazine in very small doses.

TB: Is olanzapine the only one among the new drugs that is used?

KH: Others may be used, but there are no double blind studies.

TB: Let me go back in history. At the time you started, people hardly knew of anorexia nervosa and the field expanded rapidly.

KH: It certainly did.

TB: When did the change start?

KH: Well, at first, the media was a tremendous help in increasing our business. They somehow caught onto this and started presenting beautiful movie stars, such as Jane Fonda and Princess Dianna, as having bulimia nervosa. Then it had the opposite effect. The young teenage patients would say, "Well, you know, Jane Fonda hasn't had such a bad life. Despite her bingeing and vomiting, she still is very attractive and she has married multimillionaires." The same with Princess Diana; it didn't help at all. The media always meant to dramatize these illnesses.

TB: When did the media get involved?

KH: In the late 1980's. They were totally attracted, as you can imagine, to the dramatic aspects of eating disorders. When they interviewed me, they wanted to see patients and the dramatic aspect. They never wanted to listen to the rather grim outcomes and criticism of the different kinds of therapy, or the fact that treatment centers that had no qualifications, whatsoever, were springing up all over. Our country has no restrictions on psychotherapy. If you are a physician, you have to be licensed. If you are a clinical psychologist, you have to be licensed; but anybody can set up a shingle as a psychotherapist. That is what has happened in the field of eating disorders. All sorts of crazy things are going on that are totally unregulated. The media loves it. They go to the most infamous center in Vancouver, Canada, where a lady bought a Charles Adams type house and, with her family, started treating anorexia nervosa patients.

TB: What did she do?

KH: She did what she called love therapy, but word came out that it wasn't completely love therapy, and there were problems. Eventually, the Canadian government investigated her, but ABC television thought it was wonderful.

TB: What does it mean, love therapy?

KH: Spending a lot of time with the patients, establishing what she considered a love that their mothers hadn't given them, a kind of passionate understanding that they hadn't received in their lives. Patients flocked from all over Europe and the US, but it was only wealthy clientele, because the costs were enormous. I have found, in my experience, that extremely wealthy people dictate their treatment. If you don't allow that, they are not interested. They go to totally unqualified people. This woman in Canada did not even have a BA degree. We have a person like that in New York City that was promoted by the media. He had no degree in anything. The media loved that. They promote these people because they have charisma. It's very exciting, but the rest of us who have done research tend to be rather boring.

TB: At a certain point in time, eating disorders entered the universities. At Vanderbilt, our chairman, Mike Ebert, is an eating disorder specialist. There are a steadily increasing number of eating disorder specialists. Is that just in North America, or do you see the same thing all around the world?

KH: That has happened in all industrialized countries. An interesting comparison is the island of Taiwan, with mainland China. In Taiwan, the prevalence and incidence of eating disorders is the same as Western Europe and the United States. In mainland China, in the 1980's, when I was there, they could only identify three cases of bulimia nervosa in all of the psychiatric clinics in Beijing. Now that mainland China is becoming more industrialized, there are interesting changes occurring. There are health clubs set up, in which women keep themselves in shape, but actually they are dieting and trying to stay slimmer, because now that people are not starving, they are gaining weight, and this is upsetting a large population of females. We are now seeing the incidence and prevalence of eating disorders increasing in mainland China. So it seems to be associated with industrialization.

TB: What would happen if the film industry changed the image of women to create a different kind of heroine?

KH: I think if the entire value system of beauty changed throughout western civilization, it would have an effect. Most of us who have done clinical work and research in this area for years understand that the provoking stress in developing both bulimia nervosa and anorexia nervosa is dieting. Even though you may have the genes and biological vulnerability to develop these illnesses, you won't develop them unless you start dieting. So, dieting is the major stress event for vulnerable people.

TB: So, vulnerability is influenced by dieting behavior?

KH: Exactly, because if you can stop the dieting behavior and return to normal healthy eating, then they get over it and stay over it. But, if they become concerned again about their appearance in complex ways connected to their competency to deal with life, they resume dieting. If you can get them to stop dealing with stress by dieting, they will stay healthy. Thirty years ago, there was a significant difference with the upper and upper middle classes having a higher prevalence. That has changed. Today, the difference is not even present in some countries. In the New York area, for an example, twenty years ago we never had a Hispanic in our program with anorexia or bulimia. Now, there has been an enormous increase of both anorexia and bulimia in the Hispanic population.

TB: So, at this point, it is widespread?

KH: It is across all social groups.

TB: During these thirty years, you trained many people. Would you like to mention just a few of them?

KH: I wish I could say I had many famous researchers. That has not been the case. Most of the people I have trained have gone into clinical practice all over the Metropolitan area and throughout the country.

TB: So, they are mainly practitioners.

KH: I have trained two young men who went to pharmaceutical companies, and they are both doing very well, making about 5 to 10 times my university salary. One is very nice to me, and we sometimes collaborate. He was with Lilly, and he is now with Pfizer. With Lilly, Steve Romano and I set up a huge multicenter study of fluoxetine in bulimia.

TB: So, Steve Romano was working with you in the fluoxetine study?

KH: Right. That was a one year study, one of several studies.

TB: You talked about your finding with fluoxetine. What about findings in the other studies?

KH: Our first study, and many of the other studies were NIH funded. Most of my studies have been from NIMH or Foundations. Pharmaceutical companies provided the medications. We have just finished a multi-site study on sibutramine for the treatment of binge eating disorder, but those results haven't been completely analyzed, so I can't tell you the results. Binge eating disorder is similar to bulimia. The big difference is that in binge eating disorders patients don't compensate the calorie intake by severe dieting or vomiting or laxative abuse. So, about 90% of that population is obese. The trial with sibutramine was to see if we could institute control of the binge eating episodes, which might then regulate their weight.

TB: Have you been involved in developing guidelines for the treatment in these disorders?

KH: Yes, I have been. As you know, the guidelines are produced by the American Psychiatric Association. That is a complex phenomenon, because in my field, there is a large contingent of psychoanalysts and psychodynamic family therapists. I have been rather outspoken about the fact that we need to look at the evidence from controlled studies. I was disinvited from the last guidelines committee because I wasn't empathetic enough to allow guidelines recommendations that had no proven efficacy, not even single case studies analyzed in a structured way. I think this is a very good question, because I can't believe it is unique to my field.

TB: So, people who are psychodynamic are still involved in your field of work?

KH: Yes, in my field. I can't speak for other fields, but I think it is important for us to examine who is producing guidelines. Maybe the American College of Neuropsychopharmacology ought to produce their own guidelines, because the American Psychiatric Association is highly political. Those guidelines often include suggestions that are not always supported by evidence based trials.

TB: That is very important to know. When did you get involved with ACNP?

KH: I got involved with ACNP in the early 1980s, with the first multi-site collaborative study.

TB: Have you been attending the meetings regularly?

KH: Since the early 1980s. I was admitted as a member, in 1984 or 1986, about that time.

TB: Have you served on any of the committees?

KH: I have served on the Education Committee and on the Program Committee. Right now, I have been having a very exciting time on the Credentials Committee.

TB: Have you been involved in writing or editing books?

KH: I have edited two books. One was on a meeting that was conducted by the New York Academy of Science that was published in the late 1980s. The other book I edited was the Proceedings of the American Psychopathological Association meeting, when I was president, and the topic was the psychobiology and treatment of the eating disorders. It was published in the mid 1990s.

TB: Is there anything that you would like to add?

KH: You were very thorough in questioning me. I think the future direction of research in the field of eating disorders now lies in the genetic research aspect.

TB: Didn't you start your career in genetic research?

KH: I started with Zellweger in genetics and, now, I am not going to say at the end of my career, I am back to genetics. When I first had the invitation to be interviewed my response was, "Oh dear, I am one of the over the hill people now, the grandmother of my field." I was a little bit jarred by the invitation.

TB: I'm glad you came. How much of your time are you spending in clinical practice and how much in research?

KH: It is pretty much 50-50. I manage a huge clinical operation, which is profitable to the New York Presbyterian Hospital, or I wouldn't be here. That is my big task. To see that operates effectively, I need to have hands on control. There are very few of us across Europe and the U.S. who have been trained to do this effectively. We need to oversee the direct operation.

TB: However fast the eating disorder field is growing, you probably still know most of the people involved?

KH: I know everybody who has federal grants in the research programs. I certainly don't know everybody who is treating patients.

TB: You are fully active and it seems that you intend to continue with your research.

KH: I am fully active and I intend to stay fully active for a long time. My Chairmen should take note of that!

TB: You still would like to see evidence based guidelines in your field. Thank you very much for sharing all this with us.

KH: Thank you.

28. ERNEST HARTMANN

TB: This will be an interview with Dr. Ernest Hartmann³⁰ for the Archives of the American College of Neuropsychopharmacology. We are at the Annual Meeting of the College in San Juan, Puerto Rico. It is December 9, 2002. I am Thomas Ban. Let's start from the beginning. When and where were you born?

EH: I was born in Vienna, Austria, in 1934. My family is Austrian and Swiss. My father was a psychoanalyst, a student of Freud. As a matter of fact, I met Sigmund Freud when I was two years old. He was eighty and I was two.

TB: How old were you when you came to the United States?

EH: I was seven.

TB: Could you tell us something about your education?

EH: I lived in New York and went to school in Chicago. On the one hand, I wanted to be a theoretical physicist. But, on the other hand, I was also a poet. Medicine was a compromise. I found psychiatry or neurology the most interesting, but since my father was a well-known psychoanalyst, I felt that would be too much following in his footsteps. I was at Yale Medical School and I got involved in cancer research for my dissertation. After med school I spent a year at the Institut Gustave Roussy, in Paris, doing some early research with immunoelectrophoresis in cancer.

TB: When was that?

EH: From 1958 to 1959. After my return to the U.S., I did a residency in psychiatry at Harvard at the Massachusetts Mental Health Center. I had three very important mentors there: Elvin Semrad, a psychoanalyst, Milton Greenblatt, an early psychopharmacologist, and Jack Ewalt, who held things together as an administrator.

TB: So, one of your mentors was Milton Greenblatt?

EH: Yes.

³⁰ Ernest Hartmann was born in Vienna, Austria in 1934. He received the M.D. from Yale School of Medicine in New Haven, Connecticut. After his residency in psychiatry at the Massachusetts Mental Health Center at Harvard School of Medicine in Boston, Massachusetts, he served a fellowship in the Intramural Research Program of the National Institute of Mental Health in Bethesda, Maryland. He, then, returned to Boston to work at the Boston State Hospital. Hartmann died in Boston, Massachusetts in 2013. He was interviewed in San Juan, Puerto Rico on December 9, 2002.

TB: What did you do after your residency?

EH: I spent two years in the Intramural Program of NIMH, where I worked with Lyman Wynne, and Fred Snyder, an early sleep researcher. I'd always been interested in dreams, including my own. I completed a project on dreams with Justin Weiss, a well-known psychologist, while I was still in my residency. We studied whether a dream induced by hypnosis, was similar or different from a night dream. Of course the EEG's are quite different.

TB: Did you publish your findings?

EH: We published only an abstract.

TB: When did you get interested in sleep research?

EH: I got interested while still in my residency, when Chuck Fisher, a psychiatrist and psychoanalyst, reported that some patients who developed schizophrenia had over four hours of REM sleep per night. His findings seemed to fit with theories about the relationship between dreaming and schizophrenia. Although it turned out that Fisher's data were completely wrong, they got me interested in REM sleep. I followed up his findings at the NIMH. In a long-term, controlled sleep study with dream collection, we found that the amount of REM sleep is changed in mental patients.

TB: When was this research done?

EH: In 1963 and 1964.

TB: Were you involved in psychoanalysis in those years?

EH: Well, I became involved with psychoanalysis after I went back to Boston, in 1964. I had a career investigator development award from NIMH that helped to support my research, and also paid for psychoanalysis.

TB: Could you tell us more about your research at the NIMH?

EH: I was involved in many studies. In one of these investigations, for example, we studied the changes in the sleep pattern of patients with manic depressive illness. I published a long paper with Biff Bunney on a manic-depressive woman who had forty-eight hour cycles, shifting from mania to depression or depression to mania every 24 hours. The switch from depression to mania always occurred in sleep. She generally woke up manic every other day. A few times she woke up from a nap manic in the daytime. On one occasion, I was able to demonstrate that the switch to mania clearly occurred after a long REM sleep period.

TB: You did this research with Biff Bunney?

EH: I worked with Lyman Wynne and Fred Snyder, and also Biff Bunney. Biff took overall care of our patients. He was in a sense my Chief Resident. He ran the ward, but he was also starting his depression research.

TB: Any other research you did at NIMH?

EH: I also did some studies at NIMH on how the mind is organized during REM sleep, by giving people psychological tests just after awakening from REM and NREM sleep. These studies were recently redone by Bob Stickgold, at Harvard, who found the same thing, with much better equipment. The finding was that the brain is organized differently during REM sleep; connections are being made more broadly, more loosely, than in NREM sleep.

TB: You told us that you had a career investigator development award after you left NIMH. Could you tell us about the research you did after you returned to Boston?

EH: I was hooked on sleep research and I was undergoing psychoanalysis. I was interested in connecting basic biological research with psychoanalysis, and psychiatry in general. I actually wrote a paper, in 1970, entitled, "The Biology of the Mind." I was interested in what might underlie primary process thinking, defense mechanisms and so on. I followed it up with a number of research papers, but I'm not sure how much impact it had.

TB: Did you go back to work at the Massachusetts Mental Health Center?

EH: I went to work with Milton Greenblatt at the Boston State Hospital. He was wonderful. I met with him every week or two and we found connections between my interests and his, and he always asked wonderfully perceptive questions. And then, Jon Cole took over from Milton Greenblatt at Boston State. He was an excellent director, too.

TB: Did they have a sleep laboratory at the hospital?

EH: No, there was no sleep laboratory there, when I came. I set up the sleep laboratory at Boston State. I did human studies and studies on rats, as well. But now that you've refreshed my memory, I remember that I did test some specific neurochemical hypotheses about changes in norepinephrine and serotonin after REM deprivation, in rats. These convinced Danny Freedman at Yale to work with me on the project. I used to go down to New Haven with a research assistant, and we deprived rats of REM sleep. We found interesting changes in serotonin and norepinephrine levels, but not exactly the changes we expected.

TB: Would it be correct to say that you used REM sleep as a means to test relationships between psychoanalytic concepts and neurochemical changes?

EH: Yes, you could say that, though it's a big leap. I am not a neurochemist, but I worked with people who measured biochemical changes. I did long term sleep studies in schizophrenics, and I did long term sleep studies with psychotropic drugs. I did a study that involved twelve hundred nights of recorded sleep, in which we studied the effect of five prototype psychotropic drugs and placebo.

TB: Could you name us the drugs?

EH: Chlorpromazine, reserpine, amitriptyline, chlordiazepoxide, chloral hydrate, and placebo. Each subject received each drug for a month, and each month of drug administration was followed by a one-month drug free period. Thus twelve months for each subject. Long study!

TB: When was this study done?

EH: In 1968, 1969, and 1970. By then I was a member of the ACNP.

TB: When did you become a member?

EH: After Milton Greenblatt left and Jon Cole became the superintendent of Boston State. He was very interested in pushing research, and he was also very enthusiastic about the ACNP.

TB: You did some of the classical studies in sleep.

EH: I did studies that I don't think are specifically psychopharmacological, but which are considered to be classical studies in sleep. I studied the effects of sleep deprivation on REM; then I compared REM sleep in short, ordinary, and in long-sleepers.

TB: What did you find?

EH: I found huge differences in REM sleep, but not in Stage 4 sleep, between the long, short and average sleepers. Then we studied the relationship between sleep and psychological functions. We found that short sleepers were smooth, efficient, well organized people and if they had any psychopathology, it was hypomania. Long sleepers were the opposite; they were worriers and took life very seriously. They worried about everything. We hypothesized that people who worry a lot need more REM sleep than people whose life is smooth. We tried to put it in computer terms, that short sleepers seem to be pre-programmed: their lives are organized, and run efficiently, whereas long-sleepers are weakly programmed and need to re-organize their lives every day. Thomas Edison was a well-known short sleeper; he was very well organized. He prided himself not just

having ideas, but also of being able to put them into practice immediately. Albert Einstein, much of his life, was a long sleeper. He was a deep thinker, and he worried a great deal, about humanity, war, etc.

TB: When was REM sleep first described?

EH: In 1953, Aserinsky and Kleitman in Chicago conducted the first REM studies. I was at the University of Chicago at the time but did not know much about their work. However, a good friend of mine was one of their first subjects.

TB: So research in REM sleep started in the fifties.

EH: It was started in the mid-fifties and really became known in the late fifties. When Dement and Fisher published papers on the effects of dream deprivation, in the early 1960s, that was when it really took off. I was one of the first people involved. There's some dispute about who gets credit for what. But certainly, it was Dement, Jouvet and I, who came up with the idea that the dreaming state, the D-state (now called REM-state), is not just a different kind of sleep, but it's a third state of existence. Waking, non-REM sleep and REM sleep are totally different states in many ways. I was very involved in pushing the idea that each state was different. I published a summary of the differences, in 1962–63. In waking, we have overall high activation and good feedback, and in the REM state, we have high activation with very poor feedback. We have very good studies by Rechtschaffen as to why animals die of REM deprivation – rats die after extended REM deprivation – but the best he could come up with was that temperature regulation goes off. I believe thermoregulation is just one of the homeostatic systems that are restored during REM sleep.

TB: Could you elaborate on norepinephrine and sleep, both in animals and humans?

EH: I came up with the summary idea that medications which increase norepinephrine levels in the brain decrease REM sleep, and conversely those that decrease NE act to increase REM. It's very hard to increase REM sleep, but I found it persuasive that decreasing norepinephrine would increase REM sleep. This, with other research, led to a whole theory of the functions of REM sleep.

I also did studies with tryptophan that seemed to be very important, at that time, and did turn out to be important, clinically, more than theoretically. I just walked in to a session here at this ACNP meeting today and someone said to me, "Oh, are you the Dr. H. who did all the tryptophan studies?" Some people know me just from those studies. For years in the 1970s and

1980s, I worked with tryptophan. It turned out that tryptophan was a good sleeping pill and, of course, it was a “natural” sleeping pill. This was in the late 1970s and early 1980s. In some countries, tryptophan is on the market and used as a sleeping aid. I think it is on the market in Canada, but I’m not quite sure.

TB: In Canada it was also used as a mood stabilizer.

EH: Right. I showed that it reduced sleep latency. I had patients who did very well on tryptophan. Then tryptophan ran into problems in the United States; some patients developed eosinophilic myalgia and the FDA thought it might be due to tryptophan. Much more likely, it was due to a contaminant, but as you know, tryptophan was removed from the market. It’s still almost impossible to get in the United States. I had some patients who would go to Canada regularly to get their tryptophan.

TB: When did you get back to your research in dreaming?

EH: In the 1980s, I again became interested in dreaming, partly because my clinical patients with schizophrenia often had a period with intense nightmares before they became psychotic. I also had some patients and some friends who told me they had nightmares every few days for years. So I did a study in which I interviewed many people who had life-long nightmares.

TB: What did you find?

EH: These people had “thin boundaries” in terms of thinking and feeling, and in numerous other senses. Some people never let their feelings get in the way of their thoughts. But these people had the opposite. They asked me how one could possibly imagine a thought without feeling. So I developed my concepts about “thin and thick boundaries.” I wrote a book about *Boundaries in the Mind* and many papers.

TB: What is the title of your book?

EH: It’s called *Boundaries in the Mind*.

TB: When was it published?

EH: The book came out, in 1991. And that was very exciting. There have now been over two hundred papers published on boundaries, and we have a 138-item Boundary Questionnaire about different kinds of boundaries. We have done a lot of work with that. In the last years, I’ve been doing not so much laboratory sleep research, but research on dreaming. I’ve done work on dreams after trauma and dreams in stressful situations.

TB: Stresses of everyday life?

EH: No. Stresses of people whose house burned down or people who were raped, attacked, robbed or who lost someone close to them. There are emotional concerns clearly involved in dreams, but most dreams are so complicated. I can't blame some people for thinking that dreams are just junk thrown together. But I never believed that dreams were just random.

The easiest place to look at that question would be in those people who have just experienced a trauma. The feelings in those people's minds are I am scared; I'm terrified; I'm overwhelmed. So, what do they dream about? Sometimes the dreams are about the actual event; but the most common finding is that they don't dream about the event or dream about the event only once or twice. Then they have a dream something like; "I was on a beach and was swept away by a tidal wave or a whirlwind." It's amazing how common those kinds of dreams are. I've heard that many times. I have statistics showing that those dreams are more frequent following the trauma.

See, most dreams you don't remember. So much stuff is being thrown away or thrown together in dreams. But here, you have someone who has just escaped from a burning building in western Massachusetts, who hasn't been anywhere near the ocean in many years, and whose dream is; "I was on the beach and a huge tidal wave swept me away." For me, that is very important, and I have been studying that. Such a dream is a paradigm: obviously the man is not dreaming about the events themselves that occurred. He's picturing his emotion; "I am terrified; I am overwhelmed."

It's not easy to study dreams; you have to work with what people tell you. But I have found people who write down all their dreams, like me, and who are willing to share them. I've done several interesting studies on dreams including one that's about to be published on dreams before and after 9/11, 2001. All of us were traumatized, or at least stressed on that day. There are studies showing that some symptoms of trauma occurred more often if you lived in New York City than if you lived in California. We found 44 people who had been recording all their dreams every morning, for years. Each sent me twenty dreams; the last ten dreams in their records before and the first ten dreams after 9/11 and we did a series of dream analyses.

TB: What did you measure?

EH: We selected the Central Image, the tidal wave for example, and measured its intensity in these dreams with our rating scale. There were slight, but not highly significant differences in content before vs. after 9/11. The highly significant difference was in the intensity of the Central Image. What we found was that after 9/11, people had more intense Central Images in their dreams. And, insofar as we can generalize, we all had more powerful dreams after 9/11. When we are emotionally aroused, we dream more intensely. But we do not dream specifically of the events; there was not a single dream of planes hitting towers, or anything close to that! So, that's what I have done recently.

TB: Are you still fully active?

EH: Yes, I'm active; I'm practicing part-time and I'm doing dream research part-time. I don't have a sleep research laboratory and I don't have a big grant.

TB: So, you don't have grants any longer?

EH: But this kind of dream research, you can do with students and people interested in dreams.

TB: What kind of practice do you have?

EH: In the past it has been long-term psychoanalytic therapy, but in recent years it is mostly sleep disorders medicine. I see some psychiatric patients, but I have to admit the ones I'm most interested in are patients with nightmares or psychiatric patients with sleep problems. What I see most commonly at the sleep center is people with sleep apnea and sleep problems.

TB: So you see patients mainly with sleep problems.

EH: Well, as I said, in the last years it's been more sleep disorders. For a time, I saw some long-term patients in therapy and I did some psychopharmacology. It was never a major interest of mine.

TB: Still, you have contributed to the field. Could you tell us more about your research in psychopharmacology?

EH: Let me think. Well, the tryptophan research involved many different studies. It led to studies of other amino acids, especially the ones that compete with tryptophan. We did several in normal subjects and have shown that tryptophan produces a daytime tendency to sleepiness, whereas phenylalanine produces the opposite effect. I did one psychopharmacological study on nightmares in the 1970s. It was a fairly small and not very impressive study; but it is the only placebo controlled psychopharmacological study of dreaming.

TB: Could you tell us more about that study?

EH: My hypothesis was that dopamine had something to do with nightmares. It was done in a group of normal subjects. Each person went through two nights in which they were given LDOPA and two nights in which they were given placebo.

TB: What was the dose of L-DOPA that was given?

EH: It was five hundred milligrams of L-DOPA, given twice during the night, timed so that it would have its effect at the next expected REM period. We found that dreams after L-DOPA were more vivid, detailed and exciting. We also found more nightmares after L-DOPA compared to placebo.

TB: Any other studies in psychopharmacology you would like to talk about?

EH: I studied over-the-counter sleeping medications, antihistamines, as well as analgesics.

TB: You have published many papers in the past decades.

EH: I've written and published about 310 papers.

TB: And several books.

EH: Nine books. I like writing books. The first book was *The Biology of Dreaming*. One early book was on adolescents in a mental hospital. That had nothing to do with my sleep research. In my book on *The Biology of Dreaming*, I summarized my early phylogenetic studies: I did sleep studies on the elephant, on rats, and on humans. Others had studied cats and mice. I wanted to study elephants, which are obviously at the opposite extreme from the mouse in terms of size, metabolic rate, etc. These studies were cited a great deal. I demonstrated that the dream-sleep (REM/non-REM) cycle is a basic cycle of the mammalian body. I did some studies, published a paper and a book, in which I showed a clear correspondence across species. We find the same shaped curve – covering data from the mouse to the elephant – in the pulse cycle, respiratory cycle, gestation period, and in the REM/non-REM cycle. The longest cycle is always seen in the elephant and the cycle length is inversely related to the resting metabolic rate of the species. That was published in several papers and in *The Biology of Dreaming* (1967). Then, *The Functions of Sleep* (1973) was an important book of mine summarizing many studies leading to a theory of the functions of sleep.

TB: What do you think the function of sleep is?

EH: Overall, we don't fully know. But I put forth a number of hypotheses, which are still being debated. I believe that sleep, especially REM sleep, is involved in the restoration of norepinephrine-dependent systems, which are necessary for feedback regulation in the central nervous system and in the entire body (homeostatic systems).

TB: What about functions of dreaming?

EH: There is no consensus on the functions of dreaming. I believe that dreams are hyperconnective, making connections that are guided by the dreamer's emotion. I believe that dreams weave in new material, integrating it with existing memory systems. Among other things, this weaving-in of traumatic material for instance makes a subsequent event less traumatic.

TB: How about your work on "boundaries"?

EH: My group has done a great many studies on *Boundaries in the Mind* and we developed the Boundary Questionnaire taken by more than 10,000 people. Many psychologists are using my concepts about "boundaries" and I would like to get some brain imaging people to study the difference in people with "thin" and "thick" boundaries, to see what the differences are. I would expect major differences, but I haven't done the experiments.

TB: Is there anything else you would like to talk about?

EH: I have a feeling I've talked too much. You got me reviewing my work and I have a feeling I've tired you out.

TB: We covered many areas in your research from psychoanalysis to psychopharmacology. Let me ask you: Did you use the sleep EEG in screening for psychotropic drugs?

EH: No, I didn't use sleep EEG for that purpose. Fink did a lot of that kind of work. I pride myself that I have almost never done any research for a pharmaceutical company.

TB: Never?

EH: Almost never. Once, I got some money for doing research with tryptophan.

TB: What's your opinion of ACNP?

EH: I think ACNP is a wonderful society. The meetings are exciting. I always learn something new. However, I think there is too much influence by the pharmaceutical companies, especially in recent years.

TB: Were all your research projects supported by NIH or NIMH?

EH: Almost all.

TB: Didn't you do research in narcoleptic patients?

EH: Yes, a bit. Narcolepsy, in most cases, begins at the age of sixteen, seventeen or eighteen, but is not diagnosed until age twenty-five or later. I suggested that the onset of nightmares in adolescence can be an early sign of narcolepsy.

TB: Didn't you do research also with cocaine?

EH: I don't think so. However, I did several studies on amphetamine addiction. We studied norepinephrine, dopamine, and serotonin and their metabolites in people addicted to amphetamines, and we did sleep recordings while people were on amphetamines and after they got off.

TB: Let me shift and ask you about your membership and activities in societies.

EH: I have been very active in the Sleep Research Society. I have sometimes presented papers at meetings of the American Psychiatric Association and several psychoanalytic associations. Since 1985, I've also been very active in a new society, called the Association for the Study of Dreams, that's a pure Dream Society. I'm trying to push that society to become more research oriented.

TB: Have you been active in the ACNP?

EH: Yes, somewhat. I was on several committees, including the Credentials Committee.

TB: Is there anything you would like to see to happen in the future in your area of research?

EH: That's a very good question. Here's one area; as mentioned, I've done a great deal of work on "Boundaries." We've gone all the way from psychological boundaries in individuals to how nations get along with each other. People who have "thick" psychological boundaries tend to think in terms of "thick" boundary peace; whereas, people who are a little more loose and flexible can think of "thin" boundary peace. I would love to have people with equipment to do brain imaging collaborate with me in this research on psychological boundaries. I am certain we would find clear differences in the spread of activation in the brain, especially in the cortex.

TB: So, I think on this note we should conclude this interview with Dr. Ernest Hartmann. Thank you very much for sharing with us this information.

EH: Thank you very much. You really got me talking!

29. GEORGE R. HENINGER

TB: This will be an interview with Dr. George Heninger³¹ for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College in San Juan. It is December 7, 2003. I am Thomas Ban. Let's start from the very beginning. Would you tell us when and where you were born, brought up, and something about your education?

GH: Sure. One of the psychological threads through this was that both my mother and father were strong Mormons when they got married. My father had been raised as a farmer, but sort of discovered education; so he was going to school intermittently as he was farming. He met my Mother and they got married. After he finished college, my father went to the University of Chicago for medical school. So my brother and sister were born in between there. I was the third child, born in California during internship in Los Angeles County Hospital. There was a polio epidemic at the time.

TB: What year?

GH: 1934.

TB: '34.

GH: They eventually went to Phoenix for a little bit of private practice, then back to Salt Lake City for a couple of years, where my younger brother was born, and ultimately we moved to Provo, Utah, where he became superintendent of a mental hospital, a position he held for the rest of his life. And that's how I essentially was raised, from the age of 5 until I went off to college. The reason for choosing psychopharmacology came from maybe two or three dimensions. My father studied with Ralph Gerard in Chicago, but had to feed his family, so he gave up research to practice, but he was always going on about how important research was. So that was always in my head. As a senior in high school, I had a project on antibiotics. They had just invented penicillin and streptomycin. So it was a miracle story of drug discovery and application. It saved a huge number of lives.

TB: This would be in the early 1950s.

³¹ George R. Heninger was born in Los Angeles, California, in 1934. He trained in psychiatry at the Massachusetts Mental Health Center in Boston MA. He was interviewed in San Juan, Puerto Rico, on December 7, 2003.

GH: Yes, that would be 1953. The idea that you could do research on the way chemicals altered body function was a major issue. I went to the University of Utah, in 1953. I was going to be a PhD biochemist, and I came down with rheumatoid arthritis as a freshman, which threw me off the schedule. I couldn't make all the classes. So, instead, I just went to three years of college, and then, right into medical school. And they let us do that in those days.

TB: So, three years of college and then medical school.

GH: In medical school, I started off in the laboratory of Dixon Woodbury. So the Goodman and Gilman was there, and Dixon Woodbury was a major player. And we studied the effects of carbonic ion hydrases in anticonvulsants. That was my first study. And I worked in his lab all three summers that I was there, which got me started. I did well in medical school, so I was able to get the best internship from our class, which meant you could either go to Hopkins or to Boston City Hospital. I picked Boston City Hospital because at the time I had just started reading a few papers, maybe some of yours, in psychopharmacology. So it kind of came out of anticonvulsants that I went into psychopharmacology. And I chose Mass Mental because of Al DiMascio and Gerry Klerman. So, I specifically targeted Mass Mental after my internship for training. And as a matter of fact, I worked all three years with Al DiMascio and Gerry Klerman on their clinical neuropsychopharmacology research unit. I also did my clinical training; I was a chief resident there. And that launched me on a career of clinical neuropharmacology. I had two years in the government because of the Vietnam War and public health service, and I was at St. Elizabeths with Fritz Freyhan for one year, and then I was at the Clearing House for Mental Health Information Center for a year.

TB: You worked with many distinguished people in the field.

GH: Well, the one I miss the most is Al DiMascio. He was a unique character. I've never met anybody like him before or since; very gregarious, robust, Italian, overweight, unstoppable. He didn't have a Ph.D. when I started working with him. He got that a little bit later. But he had the idea that you could use drugs in healthy humans, look at their behavioral profile, and then you could predict what those drugs would do in illness. We were using, and that was 1960, some of the first neuroleptics and antidepressants in the country. Mass Mental Health Center, where I trained was very, very analytic. Gerry Klerman sort of straddled the boundary. Al didn't get caught up in the politics or anything. He just went ahead with his research and submitted

applications for grants. I couldn't think of a better person for a young investigator to work with because he was so giving. I attended the ACNP meeting, in 1961, with Al. I think it was about the second meeting. He always took me there. And he would include you in his research. I did the legwork in Gerry Klerman's and Al's study in which they gave some drugs to healthy subjects. In one study, by accident, they got a bunch of athletes from Tufts, and a bunch of bookworms from Harvard, and they found different responses. So they thought that personality affects response to drugs. What they found was that athletes that were mesomorphs and very active would not enjoy sedative-type side effects, and that the leptosomatic, skinny, bookworms, wouldn't mind being sedated. It kind of came out that way. But we gave 400 mg of chlorpromazine orally to young men, and they went to sleep on the floor from it. It just knocked them right out. The idea of another study we did was that desipramine was quicker acting than imipramine because it was demethylated. And we compared the pharmacological profile of the drugs in normals, and what showed up, was the anticholinergic effects of imipramine. Dry mouth and all of the anticholinergic effects were prominent with imipramine. So that gave me a good start. Mass Mental at that time was the premier residency training in the country, academically. There's no question about it. There, ahead of me was Eric Kandel. The year behind me was Herb Meltzer. In my year, it was Dick Shader. So it was just the place to be. Dick Shader ran the first comparison between drugs and psychoanalytic psychotherapy at Mass Mental at that time. Joe Schildkraut was there. So I worked with Joe Schildkraut for a whole year. It was a real good starting point. The institution itself did not support research much. You had to do it yourself. I wanted to work with these guys. Greenblatt was there. So you'd just go over there and work. The training program itself was analytic totally. It didn't have any research component to it. Anyway, that set me up with better credentials, so I got a good spot at St. Elizabeths with Freyhan. That was a little harder. Freyhan had, in my opinion, more fixed ideas. It was more of a European, a little bit more authoritarian than I was used to. He would sort of tell you what to do. He'd have categories of paranoia that were very important; to me, all the paranoia was kind of the same. For me, it wasn't important one kind of paranoia, but for him it was. I got started with Louise Speck there, who was doing research with cerebral evoked potentials. The first person ever to do that kind of research was Charlie Shagass, a member of the College. Louise Speck had the first computer used in electrophysiologic work. Anyway, we did evoked potentials in schizophrenics with light flashes.

TB: So, this research was done at St. Elizabeths?

GH: At St. Elizabeths.

TB: So, you did research with cerebral evoked potentials with Louise Speck, while you were working with Fritz Freyhan at St.Elizabeths? Did you work also with Joel Elkes while there?

GH: No. He was sort of the mentor of the whole thing.

TB: I see.

GH: Bunney and Davis and Shildkraut get credit for the monoamine theory of depression, but really it came from a guy named, I think, Dale Friend, who worked at Peter Bent Brigham Hospital. It was just across the street. He was an endocrinologist, and he gave these guys the idea that depression might be related to low metabolism in the norepinephrine system. They didn't think that up. He thought it up, and that's how the idea of the monoamine hypothesis of depression came.

TB: I see.

GH: So I worked at Mass Mental, in 1957. We were doing rating scales on depressed people on the ward, and that was my job. And when Max Hamilton came as a visitor, we met him and asked him about his scale. It was amazing that Max made this scale up out of his back pocket, just by talking to patients; he just wrote down stuff. And to this day, it is his scale that huge pharmaceutical companies use. Max just made it up in a coal town, interviewing depressed people in England, and it stuck.

TB: Did you use the scale extensively at St. Elizabeths the time you worked there?

GH: Well, I did it in most of the patients at that point. And then, I went over to work at the National Clearing House for Mental Health Information for a year, and ran the Psychopharmacology Abstracts and things like that, as a sort of bureaucrat. We also sent out surveys to find out whether people read the Abstracts. Then I got a job at Yale through Gerry Klerman, who had then moved to Yale; he was staffing a research ward and hired me and Malcolm Bowers to run the research ward. I wrote a grant while I was still at NIH. You can't submit it while there, but you can write it. I wrote it on evoked potentials in schizophrenia; and I got the grant. And because at Yale there were some people who had a bigger computer by now, I got a tape recorder that I could use for the recording the evoked potentials, and then took it to the computer and processed it.

To give history a flavor of the way things were at that time, grants were much easier to get. My old mentor, Eugene Bliss, from Utah, was on the committee that reviewed my application, and he said to me, well, I didn't think it was a very good idea, but you're a smart kid, so we thought we'd give you the money. And it wasn't a good idea, because I was going to do somatosensory, visual, and auditory evoked potentials in patients with somatosensory, visual, and auditory hallucinations. Well, you don't find people with somatosensory hallucinations. They don't exist, you know. And, few visual hallucinations are seen in schizophrenia; mostly all hallucinations are auditory. So, what actually happened is, I started doing those, and I actually ran my own lab, at that point.

One thing that had happened down at NIH, Louise Speck had gotten into spectral analysis of EEG, and I had some data from that, which I wrote up and tried to publish. In the meantime, I had set up my own system to acquire EEG and do spectral analysis. And the results that I had from her didn't fit with what I was seeing. It sort of brought home the point that you've got to do it yourself if you really want to trust the data. You know, you've got to know where it's coming from; you don't see anything in the spectral analysis you can't see with your naked eye. All what spectral analysis does, it magnifies. We did evoked potentials in schizophrenics when they were sick and then gave them chlorpromazine and they got a lot better. Nothing changed on the evoked potential. It stayed the same. The thing that I stumbled on was with manics was that they didn't respond well to chlorpromazine. It was just about the time that lithium became available.

Lithium was first given at NIH, in 1961. There were two wards at NIH: the John Davis ward and the Fred Goodwin ward. They were two competing wards. And both Davis and Goodwin gave lithium to their patients and both reported to Kety at the same time their findings. It was funny that the two guys were so competitive, that they reported it secretly. They wouldn't tell each other what had happened.

This was the year before I moved to Yale, and since chlorpromazine didn't work as well, I decided to use lithium in our subjects. So, this was the first time that lithium was used in Connecticut. And it made a profound change in the evoked response. So, I spent the next four or five years showing that the evoked response to lithium on the EEG would give you a quantified measure of the effect of the drug on the physiology of the brain.

TB: So, you studied evoked potentials with lithium?

GH: I only published a little bit of that data because I felt that my data were not perfect. We had patients talking to you with Δ -waves in their EEG. I mean, they would be in Stage III and IV sleep, but they would be sitting there talking to you, because the lithium would give you those huge slow waves. One of the unusual things lithium produces is an increase in the early somatosensory response. I thought, well, I could investigate that in animals. So, I set up another lab for research with animals.

TB: Did you have any training for working with animals?

GH: No. I had used people only before, but I was in a very rich environment. The Connecticut Mental Health Center just opened up and there was a lot of money infused. Their research ward was free care, so that was a big thing. And then, several labs were opening up. To this day it is an extremely rich training environment for young investigators. John Flynn was the director at that time, and he had a lot of animal experience. Mike Sheard was there, and he had also animal experience. So we collaborated and ended up putting electrodes in the brains of rats, cats, and monkeys. I did work for several years with implanted electrodes, to see if we could get an idea of what lithium is doing by looking at evoked potentials, and levels of lithium. Probably, in terms of my career, it was when I had the most energy; I was young and ambitious. It ended up, for me, not being that productive because I couldn't get down to the specificity I would have liked to. I needed biochemical with the physiologic measures. I got very disenchanted with evoked potentials, because we stuck in electrodes in the cortex, and if you moved the electrode 1/8th of a millimeter, the whole potential would invert or get bigger or smaller and all the huge amount of information was lost. I even got to the point of trying to record single units in monkeys, but that was technically so difficult that I gave it up. And a new approach was sort of emerging at the time. During this time, maybe for 10 years, I was unit chief on the research ward. At a certain point in time, I switched from physiology to pharmacology in my research.

The strength at Yale was Nicholas Giarman and Danny Friedman, who in 1957, set up the biologic sciences training program. That program is still present. George Aghajanian was trained under that program. Floyd Bloom was there under that program. And that program was classic neuropharmacology. All the principles of pharmacology applied to the brain, and it was just straightforward and extremely productive.

TB: After you switched from physiology to pharmacology what did you do?

GH: We started to have ideas about specific compounds targeting specific receptors. That was when we wrote the paper, "Monoamine Receptor Sensitivity in Antidepressant Drugs," and things like that. And then, it happened to be I was lucky enough to have a number of young very energetic people come in, Dennis Charney being one. And we did a whole series of studies using the best drugs we could obtain to probe the different transmitter systems, e.g., GABA, the monoamines, etc. And that was very productive. We also studied the effects of tryptophan depletion.

TB: I suppose we are now in the 1970s?

GH: We've gotten up into the late 1970s, and early '80s. I must say that was an evolution for me to get into classical neuropharmacology. By that time I had become Director of the research facilities, both the lab and the ward. And then, the notion of receptor subtypes started to come up; that brought us to the molecular level. Then, we went out and recruited John Tallman and Dorothy Gallagher from NIH to strengthen our molecular investigations. A study was designed to look at receptor subtypes in the benzodiazepine system and develop drugs for that. I was Chief of the Research Ward at Yale for 13 years, and then I was Director of the Research Facilities for another 13 years. There was a lot of politics of trying to keep your funding up and things like that.

In 1960, when I graduated, I bought a few books on psychopharmacology; there might have been four or eight books on psychopharmacology altogether. That's all there were. You didn't have to worry about the size of the literature. It was that big. You could hold it. There were some farflung, some futuristic ideas of being able to specifically alter mental function, almost like what smart bombs do in war, to target exactly.

TB: It was thought that we will have drugs that work as keys in their locks.

GH: Yes, exactly, and with real specificity. That dream is still present as the central goal of neuropsychopharmacology, and to some degree we have moved in that direction with the SSRIs. They don't have the side effects that tricyclic antidepressants do, and we can get about the same efficacy. Since we don't know the pathophysiologic pathways in mental illness, we don't target exactly the abnormality, as in diabetes or some other diseases. It was for getting there that we started, at Yale, research with Tallman, who brought in Nestler and Duman, at the molecular level. It was a movement toward a more fundamental understanding of the processes involved in psychiatric disease. For many years we haven't made a lot of progress; but in recent years, we've made progress on learning about cell loss and things like that in both schizophrenia and depression.

It's still not clear why that's happening, why stress produce neuronal loss. Then in 1993, I turned over the leadership to Eric Nestler, and Nessler was there for a while, and then, in the last four years or so, Ron Duman has been the Director. I've moved into having more teaching activities.

TB: Now, let me ask you: what would you consider your most important contribution?

GH: It would take somebody independent to judge this. I think my greatest contribution is in training people. We have 6 people that are chairmen of departments of psychiatry that trained on my unit.

TB: Who are they?

GH: Well, Dave Kupfer is the first.

TB: Who are the others?

GH: Tom Uhde, Eric Nestler, Chris McDougel, Pedro Delgado, Steve Bunney, Mark Gold, Larry Price, Wayne Goodman, John Krystal, and Dennis Charney.

TB: Would it be correct to say that you feel that your most important contribution was training these people?

GH: My major contribution is sort of like of a housewife. I defended the research unit against encroachments from the state, because they were going to shut it down. I recruited a pretty good team of people. And then, we sort of set up a milieu, an environment, in which they did very well. So, training is the best thing I've done. I would like to say I'd discovered something fundamental...

TB: Did you have a clinical practice?

GH: In residency, I was a Chief Resident on a regular unit, and I did a good job. And I had 6 trainees under me, and we did a good job there. With Dr. Freyhan I ran a clinical unit. And when I came to Yale, for 13 years, I ran the research unit. We always had three residents on that unit every year. That's where a lot of the trainees came from. Ken Kendler trained there. So there were some big names that came through there. And we took care of the patients on the unit. I had a little private practice, too. I had some patients; not a lot. I spent 10 to 20 hours with patients weekly.

TB: So you combined teaching with administration, research and clinical work. You have also published quite a few papers.

GH: Yes. There's a few more in the box that never got out.

TB: What was your first publication?

GH: The first one was probably the one we did with Louise Speck on cerebral evoked potentials in schizophrenia.

TB: When was it published?

GH: That would be in 1964, or '66. Let me correct: the first one was probably not that but the one with Al DiMascio, in which we compared in normal subjects imipramine, desipramine, and an imipramine-desipramine combination.

TB: What did you find?

GH: Well, the biggest finding was sedation with imipramine.

TB: And as you said earlier, the desipramine subjects did not have anticholinergic side effects.

GH: Well, with imipramine, it was just sedation in normals. And, of course, their tapping speed would slow down.

TB: Did you measure also perceptual changes?

GH: We measured psychomotor changes but did not use perceptual tests.

TB: Didn't you carry out also another study in normal subjects?

GH: Well, I did another one with DiMascio. We studied the relationship between personality and drug effects. We gave trifluoperazine and chlorpromazine, if I remember that right, and some of the people developed EPS. I remember we had dystonia in one kid; he was a skinny kid. It sort of interested me, because I haven't seen as many fat people get dystonia as I have skinny people.

TB: Was the dosage in the study adjusted to weight?

GH: No, it was just a straight out dose. We just gave them so many milligrams.

TB: So you co-authored your first a paper with Al DiMascio?

GH: Well, Gerry Klerman was also coauthor. The effect of personality on response to drugs was a pretty big study; it was hard for me without any prior training to do the data analysis and the statistics. So that was all new to me and Al was the only one I could talk to.

GH: Then, you also co-authored a paper as you mentioned with Louise Speck.

GH: We did that one paper with Louise Speck.

TB: One paper?

GH: One, and then another one that never got accepted. I eventually found out that the data were wrong. The numbers we had did not jive with what everybody else had seen in schizophrenia.

TB: Didn't you publish your findings with lithium?

GH: Well, I published some findings as a single author. I did the whole thing.

TB: This was the evoked potential study with lithium. Could you tell us more about that study?

GH: Well, you give an electric-shock on the wrist and that goes up and gives you an evoked potential. And in about 20 milliseconds, there's an early negative wave that is followed at about 25 milliseconds by a positive wave. If you give a barbiturate, the response does not change. At the time, I thought that was pretty profound. Now, I know that it's not as profound. The EEG slowing, even if not as specific, it is more sensitive. We did studies where we gave people placebo, then lithium, then placebo again, and then we administered psychometric tests. We were able to correlate the EEG changes with the psychometric changes. What it boiled down to was that lithium produced slowing of psychomotor performance. But if you look at depression, that does it too; depression will slow you down. You don't perform as well. And we were able to dissect out the lithium effect from the depression effect. Another thing we found out was that rodents don't metabolize lithium the way humans do. There are big, huge differences. So a lot of the work we did with lithium on rodents is un-interpretable. Cats are a little bit closer to humans in metabolizing lithium than rats, and monkeys are even closer than cats. Still, there were times when we had very high lithium levels in monkeys and no evoked response changes. It had something to do with water balance, because when we hydrated the animal, then the evoked response would get bigger. I gave up trying to figure it out. That was the time I shifted from physiology to classical pharmacology. It was hard to give up a career in evoked potentials. Later on, it was not hard to switch from neuropharmacology to molecular biology; they're the same. Another point is that our residents don't use lithium very much anymore.

TB: What are they using instead?

GH: Valproate. Valproate has been advertised and proposed by lots of people. All the speakers come around and talk about valproate and they don't talk about lithium. I think there's a spectrum of illnesses within the bipolar group of diseases and lithium has a proven track record in some of those illnesses. It's true that it has also a lot of bad side effects; worse than valproate on average, just taking everything in. I think the problem is that there's times when you need to use lithium, and young people are scared of using it because they've never used it before. Another problem is

that they do not like to monitor the blood levels. So, they would rather not measure blood levels and use valproate. But there are some people that do much better on lithium.

TB: You did quite a bit of research in depression.

GH: Yes. I chose depression because the people get better with treatment. Schizophrenia, in the classic sense, is a neurodegenerative disease. It's like Alzheimer's. I mean, nobody gets better from Alzheimer's. They stay that way. If you don't have the neurons, treatment is not going to work. But people can get 90% better from depression. I don't think they get 100% better, but 90% is pretty good. So that meant that there was a process, a biologic, metabolic process going on that was present before and not present after treatment. I had a patient who cycled every other day; one day he was depressed, and the next day he was totally normal, or a little bit hypomanic. He would do that for a month. When he was depressed, he had all the classic melancholic signs, and then within 24 hours, he would be like normal. That was written up in a paper that was published with Kupfer. It was the first paper that Kupfer published from our unit.

TB: What are your current activities?

GH: I have a training grant. I've had training grants all the way. The one I currently have is for putting the neurobiology of psychiatric disease on the Internet in such a way that it's usable by medical students and residents. We're designing a participatory program that gives them a score from which we, and also they, know how well they do.

TB: What about research?

GH: I've shut my lab but we have just looked at cytokine levels in the CSF in OCD.

TB: Have you been involved with any research with drugs lately?

GH: The last one we did was a study of ketamine, an NMDA blocker in depression. We got good results in a small sample, but nobody has replicated it.

TB: When was it published?

GH: Two years ago. Bob Berman, who did it, moved to Pfizer. We keep losing all our people.

TB: Is there anything else relevant to research in psychopharmacology you would like to tell us?

GH: I guess I would say, to have on the tape, the importance of participation of young investigators in the ACNP; to get the young people involved. There have been major changes taking place in research over the years. I got involved in research, in 1961, and I remember that I had to submit my research proposal to Daniel Funkenstein at Harvard. To do our study, I had to take a piece of

paper and get him to approve. It really upset me that some other guy would have to approve our work, as though we were going to try to hurt people, or something. Now, that has become an industry, at this point. People now are going into ethics as a specialty. And also, the FDA regulations have changed. We used to be able to get hold of drugs from the companies and give them to subjects in our research. Now, the independent investigator is caught between a huge pharmaceutical company that won't give you neither any information, nor access to drugs, and the FDA, who won't let you do anything until you get all the data on the toxicity of a new compound. Toxicity studies for a drug costs over a million dollars. So, the use of novel compounds in clinical psychopharmacology by independent investigation has almost stopped. It has just stopped. Because of those two factors, some pharmaceutical companies that were liberal initially became so conservative that they wouldn't give us access to any compounds. So some ideas have been sitting around for at least 15 years; 5HT_{1A} receptor agonists have still not been used in depressed people.

TB: Let me switch and ask you about your activities in ACNP. Do you remember the first meeting you attended?

GH: I came to the first meeting, in 1961, with Al, as I told you; and then, I came in 1964 or '65 again, and intermittently, thereafter.

TB: When did you become a member?

GH: I became a member in 1980, or something like that.

TB: Have you served on any of the committees?

GH: I've been on the Credentials Committee a couple of times. And I'm on the History Committee now; and on the Ethics Committee next year. I think those are the main ones. TB: I just have a couple of more questions to ask. Is there anything you would like to see to happen in the field in the future?

GH: What I would like to see has already happened, and I'm totally amazed. You can go on the net now and get the original publication quicker than you can get it out of your own library. I mean, I can get an article from the archives of neuropsychopharmacology quicker on my desk than I can go downstairs and go through the journal and pull it out. And it can be filed on your computer and accessed later. So, I think the information transfer is a miracle. It has really changed the world. It's instantaneous. The journals are a little slow. Their archives are slow. But, you know some

of the neuropharmacology and biological psychiatry journals are speeding up their review process. So, that's good. In general, the papers could be shorter and the information in papers larger, so that you could read the paper and get to the point sooner. It would also be good if the raw data, the actual numbers that form the basis of the paper, would be available for your computer. So you would upload that and you could do your own analysis on the information. That step is not quite yet taken.

TB: Anything else?

GH: Oh, well, yes. But they're all fanciful.

TB: Tell us.

GH: I would like to see an organization that would be above the FDA that would have health as its main concern, not just the regulatory issues, and that that organization would be able to order the FDA to give individual investigators access to proprietary information that is on file with the pharmaceutical companies. So, if I want to get an individual IND for any drug, I should be able to get all the information on it. You know, there are lots of things that just shut the individual investigator out, and I think that has really injured the rate of progress in research. I would like to see also an organization that forces all clinical studies to be public domain information. The pharmaceutical companies conduct extremely expensive and sometime dangerous studies, and none of that data is ever available to the public, to anybody. It's locked away. And there are children who are getting pharmacologic trials, little kids, and if the drug isn't effective, none of that information is available to any investigator, to anybody else. It's invisible.

TB: These are important issues.

GH: It's essentially an industry that is polluting the environment. And if you do that in a steel mill and you kill people with smoke, it's against the law. Yet, the pharmaceutical lobby will squash any attempt to change the system. So there needs to be a new organization that rewrites the law in order to make all the original information public. The information has already been obtained, it's already there. But you can't see it.

TB: Do you think ACNP should get involved in these issues?

GH: The ACNP has been unable to change this problem. I'd just put a plug in for the ACNP. The ACNP is not as important in some areas as it thinks it is, but it's more important in some other areas than it thinks it is. The Society for Neuroscience is a much bigger organization, and it

produces humongous advances. There are 30,000 to 40,000 people in their meetings and not just hundreds, as we have here. I would think the ACNP could do a little bit better by sort of enlarging itself to a little on the model of neuroscience.

TB: On that note we should conclude this interview with George Heninger. Thank you, George, for sharing this information with us.

GH: Thank you.

30. LEO E. HOLLISTER

TB: This will be an interview with Dr. Leo Hollister³², one of the pioneers of neuropsychopharmacology. We are in Nashville, Tennessee. It is April 6, 1999. I am Thomas Ban. Tell us where and when you were born and something about your childhood and early interests.

LH: I was born in Cincinnati, Ohio, in the 1920's. I was educated in that city, which had excellent facilities. I went to one of the first college preparatory high schools that was public in the whole country and then to the University of Cincinnati, which was sponsored by the city.

Whatever educational attainments I've had, I owe to the city of my birth. My medical school training was about the same as everybody else's. I'm always amazed when people rank medical schools; it's not what the school gives you, but what you put into your education.

TB: Did you always plan to get into medical school?

LH: No, the earliest idea I had was to go into law. My stepfather was a Judge in the city, and I remember, at the age of eight or nine, being placed in the judge's seat, looking over his courtroom, and being impressed by the majesty of the law and what it means to civilization. Later on, I determined lawyers spend time trying to distort the truth and physicians spend time trying to find it out. This was influenced greatly by the books of Paul de Kruif. He was a Dutchman, who was a journalist and wrote books about the early adventures of scientific medicine. One was called *Microbe Hunters*; another was *Men against Death*, which celebrated the great advances made in the 1900's, elucidating infectious and nutritional diseases and medical progress, in general. It seemed a great adventure to make such wonderful discoveries and have a profound impact on the lives of so many people.

TB: When did you graduate from medical school?

LH: I graduated about six months earlier than normally because the war came along and programs were accelerated. Our class was the first to graduate early due to wartime. Actually, I graduated

³² Leo Hollister was born in Cincinnati, Ohio, in 1920, and graduated in medicine from the University of Cincinnati in 1943. He trained in internal medicine at Boston City Hospital and the Veterans Administration Hospital in San Francisco. In 1953, he became chief of the medical service of the Veterans Administration Hospital in Palo Alto, and remained there until taking a post, in 1986, as professor of psychiatry and pharmacology at the University of Texas Medical School in Houston. Hollister died in 2000. He was interviewed in Nashville, Tennessee, on April 6, 1999.

the day before my twenty-third birthday. That gives you some idea of how accelerated things were.

TB: What year are we in?

LH: December 1943. I took an internship in medicine at the Boston City Hospital, and on the way, I was accompanied, as far as New York, by Mort Reiser, who later became Chairman of Psychiatry at Yale. Mort was taking a medical internship at Downstate, New York. It was rather peculiar, both of these Cincinnati boys leaving home the first time, ultimately for similar careers. After residency in medicine, I went into the Navy, almost simultaneously with the end of the war. I was stationed at a naval hospital in Portsmouth and one of our officers said the war would be over in two weeks. We were still island hopping in the Pacific, so I bet him ten bucks, and he won. He must have had advanced knowledge of the atomic bomb and that changed things drastically. My naval career was totally undistinguished. I was stationed in Hawaii; it was the first vacation I'd had in years, with very little responsibility and a beautiful place to be.

TB: You finished your residency in Internal Medicine?

LH: After military service, I finished residency and started a private practice, but being a member of the Naval Reserve, attached to the Marines, I was summoned back in 1950, when the Korean Conflict broke out. Again, I had a pretty soft posting assigned to the Naval Hospital in Oakland, across the bridge from San Francisco, where I lived.

TB: So, by 1950, you were in San Francisco?

LH: I'd gone there after the war to finish my training; having passed through on the way to Hawaii, it looked too good to pass up. I wound up with a wife, who was a native Californian, and produced four children. That became my home for almost forty years.

TB: Did you go back to practice after the military?

LH: No, having decided that maybe I would be called back to the military every four or five years, I thought I'd play it safe and join the Veterans Administration. There was a chap, who had a job at the V.A. Hospital in Menlo Park, near where I lived, and I had a job in San Francisco, where he lived. We decided to switch; the one he had was internist for a psychiatric hospital, a totally new experience. I thought it would be similar to practicing veterinary medicine, because you couldn't get reliable histories, and we rely on that for diagnosis and treatment. So, it was an interesting experience. While I was there, a detail man from Ciba Geigy said they had a new drug they thought

might be good for high blood pressure. Oddly enough, that had been one of my major research interests. I never published, but I'd done a lot of trials with different drugs to treat hypertension and nothing worked. So I said, "I know all the hypertensives in the hospital. If you give me some of the drug, I'll be happy to try it out." Things were so informal in those days that all he had to do was go to his car, fetch a few cartons of tablets, and give them to me. Two days later, the first patient was started on reserpine. It didn't take long for many patients to find out it was the first effective anti-hypertensive. So I was impressed. When he came back three months later he said, "We now have evidence from a specialist on hypertension in Boston that this might be good for psychiatric patients, mainly schizophrenia." I said, "Gosh, let's see what we can do." Not having any training in psychiatry, I didn't feel confident to evaluate a drug in any kind of mental disorder, so I went to the Chief of our Psychiatric Service and told him the story. Somewhat patronizingly, he said, "You know, in psychiatry, drugs have come and gone over the years, and they all turned out not to be very effective. I think it would be a waste of time." I had a streak of obstinacy, so I said, "Do you mind if I ask my golfing buddies, who are psychiatrists on staff, if they would take a look and tell me what they think?" He replied, "No, go ahead." So I asked a colleague to send patients to my medical ward; I would begin treatment with reserpine or placebo, randomly, and send them back to him for observation and evaluation.

TB: So, you did a placebo controlled double-blind study?

LH: That's right, the first of its kind in schizophrenia. At first, we didn't know what the proper dose was, because the only paper relating to reserpine in schizophrenia was a short paper by Nate Kline, with not very striking results, using the same doses given for hypertension. It turned out later on that Ciba decided the dose needed to be much higher. They had sent a physician from the East Coast to arrange studies on the West Coast for hypertension and any other indication. Based on the results, I would start patients on five milligrams by intramuscular injection for three days, follow it up by oral doses of the same magnitude for another few days, and then, taper it down to three milligrams by mouth before sending them back to their ward on active drug or placebo.

TB: Are we in 1955?

LH: This would be probably late 1953 or early 1954.

TB: So, it is before Heinz Lehmann's paper on chlorpromazine?

LH: I think it was the same time. The first study we did in hypertension was in the latter part of 1953, followed by the ones on schizophrenia in early 1954. My friends were saying, "I don't know what the hell you're doing to these patients, but something is going on. They're vastly different from how they've been before." Others seemed to be unchanged. In those days, the American Medical Association annual meeting was a big affair and there was a scientific exhibit on chlorpromazine by Mark Altschuler from Harvard. Altschuler was a professor of medicine.

I'd read stuff he'd written; a nice review on pulmonary edema and other medical topics, but I was curious how he got to study chlorpromazine and schizophrenia. It turned out that, tragically, his wife was afflicted by the illness and that encouraged his scholarly interest. He and one of his residents had an exhibit reporting on two patients treated with chlorpromazine. I remember talking to Altschuler and asking him the details. Again, things were ridiculously simple in those days. I simply contacted Smith, Kline and French (SKF) and said I'd like to have chlorpromazine to try in patients and, in no time at all, I had an adequate supply of both chlorpromazine and placebo.

TB: Didn't you do the first placebo-controlled parallel design studies in schizophrenia, with both reserpine and chlorpromazine?

LH: I think so. Joel Elkes had done, unbeknownst to me, the first crossover study, but mine was the first parallel group design ever used blindly.

TB: The psychiatrists who evaluated your patients were totally blind?

LH: Yes.

TB: Before switching to chlorpromazine, hadn't you done other studies with reserpine?

LH: Yes, a year or two earlier. Nate Kline, who always had original ideas, some rather far-fetched, decided that if reserpine was good and chlorpromazine was good, the combination would be better, which sounded reasonable.

TB: Am I correct, that you also studied the effect of reserpine in normal subjects?

LH: Yes, along with the studies in schizophrenia, I was curious how it might affect normal people. As I recall, we got nineteen normal subjects. Half got one milligram of reserpine a day for a week and the others got placebo. The placebo people complained of the trivial things you expect with placebo, but the ones who got reserpine felt like they had the flu with mild diarrhea, which was one of the side effects of the drug. But the most striking thing was that seven out of ten developed

depressed feelings. I reported that along with the early experiments of reserpine and chlorpromazine in schizophrenics.

TB: People talk a lot about reserpine and depression, but when one looks at the literature, you are one of the few who published findings.

LH: I was curious about that.

TB: It seems what you noted, as you described, was not clear cut depression.

LH: I guess we'd call it dysthymia these days.

TB: Technically, for the psychopathologist, it would have qualified as dysphoria, feeling lousy, and not for dysthymia which is having a depressed mood.

LH: Nonetheless, it was easy to see how reserpine developed a reputation, not only in psychiatric patients, but also in hypertensive patients, of being able to produce depression and there were several case reports of people committing suicide. People who are hypertensive tend to be depressed regardless of what they get.

TB: Reserpine and depression is a tricky issue. In some countries, such as Argentina and Hungary, for example, they even used reserpine in low doses in the treatment of "neurotic depression." Michael Shepherd, I think with Davies, found that in low doses it was an effective treatment for those patients. When did you first publish your findings with chlorpromazine and reserpine?

LH: I got an invitation to the AAAS Meeting, which was held traditionally in Christmas week, and in 1954, was to be held in Berkeley, which was close by. So there was a chance, for the first time, to publicize my work. At the AAAS Meeting, I gave a paper reporting on the studies we did with reserpine and chlorpromazine.

TB: So, you reported on findings in several studies.

LH: In one paper. I always tried to be economical. In those days, I was terribly naïve; I thought I was giving a paper in public and it was going to be published, so that's all I needed to say. So, I made no more mention of it. The paper was given at the end of 1954, and the book that had the paper in it appeared sometime in 1956, about a year and a half later, which is the way books are. And, of course, it wasn't read by many people. I don't know what kind of printing they had, but it couldn't have been very large. If there was a way to keep your "light under a bushel," I was doing it. I think the book was edited by a young chap named Jonathan Cole, who was a protégé of a famous neurophysiologist, Ralph Gerard, from the University of Michigan.

TB: Oh, by Jon Cole and Ralph Gerard?

LH: Gerard was a fascinating guy. He was one of these short pyknic individuals, with a round bald head and cherubic face. He always had a quip, some joke, but he's most famous for the line, "Behind every twisted thought, there's a twisted molecule." It was through his pressure that the Psychopharmacology Service Center was set up as a branch of the National Institute of Mental Health, and Jon Cole became the first Director. I'm not sure of the details but I think that this is generally true.

TB: So you first presented your findings with chlorpromazine and reserpine at the AAAS meeting in Berkeley?

LH: I'd been working in a vacuum, almost totally by myself, until at that meeting I ran into people who were in the field. I remember Dick Roberts from Ciba accompanied me to the Berkeley meeting and he recognized Nate Kline heading toward the podium. So Dick introduced me to Nate. Nate's attitude toward both of us was like we were peasants, beseeching the emperor; I was put off by it and remember saying to Dick, "Who in the hell does that son-of-a-bitch think he is? Does he think he's going to get the Nobel Prize for using your drug?" Well, that wasn't so far-fetched. Two years later, he did get the Lasker Award. It may be he wasn't so off the mark, but that was a disagreeable beginning. That was a rocky relationship Nate and I had over several years. Sometimes we were friendly; sometimes we had almost ad hominem arguments. Nate was a strange person. He always had this chip on his shoulder and he'd never miss a chance to get into an argument, even if there was a way to find some resolution. He was, of course, tremendously ambitious, which I guess we all were. That's not to fault him, but he would pick up any little idea and immediately follow it. I remember something came up from someone that copper oxidase enzyme in blood was increased or decreased in schizophrenics and Nate immediately studied it and wrote a report. A year or so later, we found it wasn't changed at all, wrote a report and that was the end of that. Nate was always willing to go out on a limb to be first and that was a manifestation of his great ambition.

TB: Anyone else you would like to mention who participated in that meeting?

LH: I ran into Murray Jarvik, who was there to talk about LSD. Somewhere in the history of psychopharmacology, the Abramson Group seems to have been lost. You hardly ever hear of them. Murray was part of the group led by Abramson in New York, which used to get together

every Friday night, and after an elegant meal, they all took LSD, did some tests while on it, and on Saturday, they'd write papers on the different effects of LSD on the various tests. There were about seven people in that group and Murray was reporting on that. Nicotine later became his major drug of interest. Another chap at the meeting, who later became a drinking buddy of mine, was an Englishman, named John Kinross-Wright. He wound up in Houston, Texas. John was a really adventurous type. His idea was if a little bit of medicine is good, then a whole lot has got to be better. He set the course record on giving chlorpromazine to people; I believe it was six grams a day. Anyway, John did do a lot of pioneer work and as a result of his aggressive treatment, he probably described the first case of neuroleptic malignant syndrome. But at that time, it wasn't recognized as an entity; I think he referred to it as an acute mid-brain syndrome.

John was also very imaginative. So, those two people stand out in my memory.

TB: You had done two placebo-controlled studies; in one you found reserpine and in the other chlorpromazine better than placebo. Did you see any difference between the two drugs?

LH: Well, the general feeling seemed to be that chlorpromazine did it a little better, a little more quickly, and a little less noxiously. You didn't get that flu-like syndrome with chlorpromazine that you did with reserpine, although chlorpromazine wasn't easy to take either. Then, of course, there was also the fact that there was no commercial advantage to reserpine. You couldn't patent a natural product, but you could patent chlorpromazine.

TB: How did you get to the idea of giving reserpine to normal subjects?

LH: I was always curious as to what drugs do in the absence of pathology, so that's why. Because of my interest in medicine, I was also interested in side effects and I had seen the first cases of acute dystonic reactions in this country. Maybe I didn't see the first ones, but I recognized them. It was my custom at the time to start off with parenteral medication, then switch to oral and we were working with the second phenothiazine SK& F had, which was prochlorperazine (Compazine). I started three young patients on it with an IM injection in the morning and by evening, when I was leaving and while I was at the nursing station, one of the new subjects came up and said, "Ahhhh, I can't talk." I'd never seen this before and nobody else had. I looked at the nurse and I said, "Well, what do you expect? He's crazy." I thought it was some sort of a bizarre hysterical reaction. In those days, the all-purpose drug was Phenobarbital, so I ordered it. I called

back a couple of hours later after I got home, and said, “How’s the guy doing?” She said, “Fine. It’s all subsided.” So, it seemed definitely to be a reaction to the drug.

One of the advantages of being in a medical area, where there’s a tremendously good medical library, is you can find out what’s been going on, if you really want to. So, I went to the Lane Library at Stanford and there was an article in *Nervenarzt*, the German neurological journal, about a year before, which told the whole story of acute dystonic reactions, covering everything. After I read that, again in my naivety, I thought once it’s in the literature it becomes generally known; there’s no use reporting anymore, because it’s all there. Of course, it wasn’t, and up until ten years later, there were still case reports of dystonic reactions appearing in the literature.

But, it was that sort of thing that would attract me.

TB: When did you work with prochlorperazine?

LH: This was about 1956. SK&F, for commercial reasons, decided to promote that drug as an antiemetic.

TB: In Canada, it was marketed as an antipsychotic. Did you do the same kind of placebo controlled parallel design study with prochlorperazine, as you did with chlorpromazine and reserpine?

LH: We were starting, but I don’t know we ever finished that study, because when SK&F decided to go the antiemetic route, I abandoned it. It was a perfectly good antipsychotic, but the reason they abandoned it was commercial. They didn’t want to compete with their own product, trifluoperazine, which they were developing. Until ten years or so ago, Compazine was a major antiemetic drug. Now, it’s been superseded by a number of others.

TB: During those years, you picked up and reported on several side effects with psychotropic drugs.

LH: Over the next several years, we had a number of papers on side effects. One of the first was hematemesis and melena, associated with reserpine. And, while one could make a case that reserpine could produce peptic ulcer, because of its parasympathetic activity, my impression was that these were gastric erosions due to increased acid. You could get a good bleed from them, but they were not the kind that continued and gave a lot of trouble. Later on, we had a report on unexpected asphyxiation associated with a number of these drugs. I was called to see one patient

in the night and he didn't have any signs of life. The idea that he died of asphyxia was a reasonable one at the time, but later on, we realized that it was probably ventricular fibrillation.

TB: Now, in addition to chlorpromazine and reserpine, you were also one of the first in North America to work with Hydergine, an ergot alkaloid, in geriatric patients, sometime in the 1950s.

LH: Oddly enough, my first psychopharmacology paper was on Metrazol in old age. I did a study on oral Metrazol, which was considered to be an analeptic drug. Now we'd call it a GABA antagonist and it didn't work. Then we did a study with Hydergine and had very good results in two patients; the others showed no change. Both of these patients had hypertensive brain disease, which we now call vascular dementia. I've often wondered why people don't think more of treating the vascular component of dementia. It used to be that vascularization accounted for about a third of old age dementias, whereas now, it's only ten or twelve percent because of the better treatment of hypertension. The vascular component is treatable even with anticoagulants or aspirin or any number of antihypertensive drugs. All of these are probably simple, safe, and relatively effective treatments. They're not going to affect a lot of patients, but they might benefit some. I think this accounts for the occasional anecdotal experience, when somebody says, "Gee, I put my grandmother on Hydergine and she did wonderfully."

TB: Weren't you one of the first who published on Hydergine in old age?

LH: I was, and I felt much more confident to be a judge of the effect of Hydergine on psychosis in the aged than about the effect of reserpine and chlorpromazine in schizophrenia. I don't remember other people working with Hydergine, at the time, but I remember several working with chlorpromazine. Yesterday, thinking about this interview, I remembered that one of the neglected names in psychopharmacology is Nathaniel Winkelman. He published, in JAMA, the first report on chlorpromazine in schizophrenic patients in the U.S.

TB: Is he alive?

LH: No. I'll tell you the story. Winkelman was son of a prominent Philadelphia neurologist and neuropathologist. He was a straight out psychiatrist of the time; SK&F, when they got chlorpromazine, was just a small company and weren't prepared to do any kind of scientific study. So they decided they'd get a psychiatrist to look at this drug, found Winkelman, and persuaded him to try it because he was local and they could keep their hand in. And, that's how Winkelman got to study chlorpromazine first.

TB: Another early investigator of chlorpromazine in this country was Kinross-Wright.

LH: I don't think he was as early as Winkelman, who had the pressure of SK& F behind him to get published. I don't remember the cause, but Winkelman died very early in life, and that's why nobody's ever heard of him; but he left his mark as the first who tried chlorpromazine. SK&F had only one drug. Since 1937, they had dextroamphetamine and they were making a living on just that.

TB: What did they sell it for?

LH: Initially, as an antidepressant, I think. It wasn't too long after, when some pediatrician found it was good for the hyperactive child, so that indication came along pretty early. Appetite suppression also came along quickly. So, there were a number of indications. Gordon Alles, the pharmacologist who rediscovered it, because it was synthesized back in 1898, had a patent on it and became the largest stockholder in SK&F. He was a big philanthropist in Southern California, making all his money on one drug.

TB: In addition to reserpine, chlorpromazine, and Hydergine, didn't you also work with meprobamate in the mid-1950s?

LH: I picked that up around 1956. I remember I paid a visit to Frank Berger and heard the whole story; how they were looking for a long lasting form of mephensin, and put two carbonic acids on either end, which prolonged its action. I got a little booby trapped by that. I thought it'd have a more specific activity than the barbiturates, but it didn't have anything special.

TB: What population did you use it in?

LH: I decided to try it in schizophrenics; that had become my major interest. We gave as much as forty eight hundred milligrams a day, which puts you at a great risk of dependence. Later on, I did a formal study of meprobamate dependence. We did see improvement, but it was more on the behavioral side. What I saw, and probably misled me, was the same thing we see today when we use benzodiazepines to curb disturbed behavior in schizophrenic patients, while using the antipsychotics to work on the psychosis. It wasn't that meprobamate didn't help, but it was not effective as an antipsychotic.

TB: It wasn't as effective as chlorpromazine or reserpine in that population. Weren't you the first to pick up withdrawal reactions with meprobamate?

LH: We did a study with high doses up to forty eight hundred milligrams. People could not go any higher without becoming ataxic. It turned out meprobamate produced a classical withdrawal reaction, the same thing that had been described by the group in Lexington, a few years before, with short acting barbiturates. We were using simple chemical measures for plasma concentrations and calculated the half-life was about eleven hours, which would put it in the same realm as short acting barbiturates. For practical purposes, meprobamate had the same kind of withdrawal reaction as the short acting barbiturates, and we applied about the same increment in dose to produce it. I don't think it ever became a major problem in clinical use because most people thought twelve hundred milligrams was a sizable dose.

TB: Then you became involved with the collaborative Veterans Administration studies, didn't you?

LH: The VA had a history of doing collaborative studies, dating from the end of World War II, when streptomycin and other drugs, like isoniazid and iproniazid, came along for tuberculosis. In those days, there were hospitals diverted to treating tuberculosis patients in a sanatorium. There were hundreds of patients languishing there, sometimes on eighteen months of bed rest. It'd kill me. I don't know how you could do that. So, the VA and the Armed Forces developed a set up, around 1946 or 1947, to study these drugs in tuberculosis. They used the double-blind technique, derived from a clinical pharmacologist at Cornell, called Harry Gold. Cornell used to have wonderful conferences on therapy that Gold produced; they were published periodically and would discuss the treatment of different medical problems. Gold was always harping on the need to do double-blind studies. In those days, he was a voice in the wilderness, because no one cooperated, but with the VA/Armed Forces study of the anti-tuberculosis drugs, that became much more acceptable.

TB: Were you involved in studies with iproniazid?

LH: No. I'd had a little experience with iproniazid, but unfortunately, in the first three patients we treated, we had a case of jaundice, and I did a liver biopsy, and showed it was typical parasitical jaundice. I remember Dr. William Middleton, the Chief Medical Director of the VA came by; he was a fascinating man, tremendously interested in every aspect of medicine and he would go into backwater places like ours to find interesting cases. I pulled up a slide and told him the story and he was very fascinated.

TB: So, you were not involved in studies with iproniazid?

LH: No, but the VA decided these drugs were important and needed to be looked at, so they asked every psychiatric hospital to nominate somebody to go to the central office to discuss this.

Our administration decided that they'd send the Chief of Psychiatry, the same guy that told me to get lost, as our representative. That didn't work, and the next meeting, a few months later, they specifically asked for me to come, and from that point on, I became closely allied with the VA collaborative studies on chemotherapy and psychiatry. That was an eye opening experience because even though I had met people like Kinross-Wright and Nate Kline, psychiatrists in the field, I had never been exposed to a great number of other people that were important. For instance, I knew nothing about psychometrics and statistics. All of these things were fairly new, but I got to meet Maury Lorr, who developed one of the first major scales for evaluating psychiatric patients, the inpatient multidimensional scale (IMDS), later refined by John Overall and Don Gorham into a brief psychiatric rating scale (BPRS), which became the most popular rating device in psychiatry. I got to meet a number of biostatisticians. I had contact with one on a follow-up study I was doing on rheumatic fever, a chap from the National Academy of Science (I can't think of his name right now); it wasn't an inferential statistic that we used, but a more descriptive approach. This was something new to learn. At the same time, I had good ideas about design, and as a result, there were a series of large scale Veterans Administration studies involving a number of phenothiazines in schizophrenic patients, and ultimately, one on antidepressants, as supplements to try helping what we now call negative symptoms, patients that don't show much motivation. The very first study was quite encouraging. We had four treatments; chlorpromazine, mepazine, not widely used but thought to be good because it didn't have many side effects, a positive placebo, phenobarbital, and an inert placebo. That study came out extraordinarily well. You couldn't have written the script any better; chlorpromazine was clearly effective, more so than any of the others. Mepazine had some effect, more than phenobarbital, and inert placebo did nothing. We were able to differentiate between two effective drugs, one good and one not so good, and I thought that was a good level of sensitivity.

TB: The studies of the Veterans Administration with antipsychotics preceded the NIMH Collaborative Studies.

LH: These were the first major multi-clinic studies and we had done two or three of them before the Psychopharmacology Service Center decided to do theirs. There have also been a few States that have done studies. I think California had one, and I'm not sure that Fritz Freyhan didn't do one in Delaware. They were all modeled after the VA studies. In 1954, there were untreated patients all across the board, but by 1956 or 1957, when we began to do these studies, the drugs had already made inroads. But we were still getting a lot of new admissions. As you know, schizophrenia takes a while to develop. One of the thoughts that occurred to me early in the game was, all these guys are veterans and some of them are as crazy as can be. How in the world did they ever get into military service? I had done a great number of clinical examinations on people entering the military and I'd never let one of these guys through. At that time, it was not difficult to get their military records. So I would dig them out to see what their first contact with psychiatry was. The amazing thing was, that these youngsters, age eighteen or so, like most young soldiers were anxious, so the diagnosis of anxiety reaction was perfectly reasonable. But now, five or six years later, they were clearly schizophrenic. I never reported this, but I was at a cocktail party about that time and Roy Grinker was there. I mentioned this experience to him and he said, "I've had exactly the same experience in civilian life. These youngsters, the nervous kids, you think are just plain nervous but in a few years, they become psychotic." That reassured me; my observation was correct, but I don't think it's widely recognized. Grinker must have published it, because he's so well established.

TB: Prodromal schizophrenia.

LH: Yes, you've got the right word. There are some things in psychiatric nosology that are completely overlooked and some that become myths, like the fact that the conventional antipsychotics don't affect negative symptoms. That's one of the biggest myths ever perpetrated.

TB: Weren't you involved in some nosological research with John Overall?

LH: John Overall and I had some interest in this for years. When we were starting off, representatives of Smith, Kline & French said, "We'll give you all the chlorpromazine free. You can treat every patient in the hospital." They wanted to see what the impact was if we saturated the hospital with it. In those days, we didn't get six figure grants for doing fourteen patients. We got nothing. Everybody was clamoring for the drug, but there was no money involved. I thought that was a pretty good deal, because even at the market prices then, it would have been a fair

amount of money for the hospital. I called up one of my best of buddies in the golfing world and one of the most cooperative and I said, “Roy, how would you like to have all the patients on the ward on chlorpromazine”? He replied, “Oh, my God, I’ve got so many patients now talking to me, who never said a word before, it’s all I can do to keep up with them.” If that isn’t treating a negative symptom, I don’t know what is. Some years later, when that idea became even more popular, the concept that conventional drugs didn’t do much for negative symptoms, I looked over data from studies John Overall and I had done. We had BPS clusters, and one was particularly strong in negative symptoms and another was strong in positive symptoms; if you compared them, there was improvement in both, somewhat less in the cluster with the negative symptoms, but it wasn’t nothing. At that time, I was in California and John was in Texas; I remember calling him up and saying, “John, our data clearly indicates what I mentioned.” I said, “I think we ought to publish something on this before this idea gets more widespread.” But, John wasn’t very entranced about going over old data. He probably had the computer files tucked away, so to get the data would have required some work. He didn’t have much enthusiasm and I wasn’t motivated to press it. So, we never did that, but there’s no question this is a myth and it’s all the more developed now because of the atypicals, which are another myth, but that’s beside the point. Let’s see, where are we chronologically?

TB: We talked about the VA studies and started to talk about your collaboration with John Overall.

LH: I stayed with the VA collaborative system from 1957 to about 1961. In 1960, I happened to run into John Overall at one of the VA annual meetings, and John (all of my friends are good drinkers) and I were polishing off some booze and coming up with all kinds of wild, interesting ideas. John was a very productive thinker and we decided to hook up and do a series of smaller, collaborative studies to keep up with the pace of drug development. We got grant support for that and it went on for many years. In the meantime, back in 1957, Nate had come up with the idea that combined drugs would be better, and I did a double-blind study with two drugs. You could do it just as easily with two as with one, using a combination of chlorpromazine and reserpine vs. placebo. Well, it turned out the combination wasn’t better, it was worse, in terms of side effects. I must confess I didn’t give it a proper trial, because we used full doses of both drugs, so it’s no wonder we got more side effects. That may have scotched the idea too early, because it died and whether we missed anything or not, I don’t know. With the advent of antipsychotics with multiple

actions on receptors, I keep thinking that maybe a pinch of reserpine plus some chlorpromazine might broaden the spectrum. But, I'm not convinced these other actions mean a damn thing, anyway. They're all still basically weak dopamine receptor antagonists and that's where the story lies. By 1957, I wrote one of the Medical Progress articles in the New England Journal, summarizing the concerns about side effects and complications of psychotherapeutic drugs, and I repeated that in 1960, and did another one in 1964, at about three or four year intervals. After that the number of new things didn't turn up that fast.

TB: Wasn't it about that time you did some work with thioridazine in depression?

LH: That idea came out of a very productive meeting. There were a lot of basic scientists there as well as clinicians. One of the things the basic scientists kept saying was that when they looked at antidepressant and antipsychotic drugs they don't find much difference in pharmacological activity. Of course, we didn't know the whole story at that time. Clinicians claimed, to the contrary, that some drugs were good for depression, and others, for schizophrenia. So, I decided to do a study comparing both kinds of drugs in both indications. I figured no matter how it comes out, I'm going to win. So, I designed a triple-blind study in carefully selected depressed and schizophrenic patients. There were two separate studies, thioridazine, which we chose because it wouldn't take away the extrapyramidal reaction, versus imipramine. It turned out that in schizophrenic patients, thioridazine was clearly superior.

Imipramine didn't make them worse, as was the myth at the time. On the other hand, in depressed patients, it was very difficult to see much difference. In Europe, there was an idea abroad that thioridazine was useful as an antidepressant. I think we might have been somewhat wrong about that, but nonetheless, it was an interesting design, because, it was triple-blind. The result was not as productive as the basic scientists hoped, but by that time, they had discovered more meaningful differences between the two classes of drugs.

TB: Do you think that thioridazine has a place the treatment of depression?

LH: If you had a psychotic depression, it might be the antipsychotic of choice. However, the combination of perphenazine and amitriptyline seems to work so well, I don't think anybody proposes it. Plus thioridazine has an anticholinergic action, as well as imipramine, so if you use the combination, you may wind up with a lot of patients who have paralytic ileus or blurred vision. So perhaps, it's just as well that combination was never developed.

TB: I think you also did some work on the effect of thioridazine on the EKG?

LH: The EKG work stemmed from the question of why some people died suddenly. We found that thioridazine was probably the worst in terms of increasing the time for ventricular repolarization, that is the duration of the QT interval, and this would increase the odds, which were remarkably small, of a re-entrant ventricular rhythm leading to ventricular fibrillation. We also found that was due to the thioridazine metabolite mesoridazine. It's surprising how much misunderstanding there is about sudden death. One of the most memorable medical papers I ever read was when I was an intern and it was by Allen Morris, the Chief Medical Examiner for Boston, who had his lab at the Boston City Hospital, where I was an intern. It had a fascinating title, Sudden Instantaneous Physiologic Death. He was describing deaths that occurred suddenly and unexpectedly, without obvious cause, where you could find nothing post-mortem. You could only die suddenly one way, and that's to have your heart stop. And the heart stops mostly from ventricular fibrillation, although there are a few cases of sinoatrial electrical disturbance instead. That explained so many things, over the course of the years. I got interested in this problem when two lawyers talked about wanting to sue somebody because a patient was sleeping with her husband who noticed, about three o'clock in the morning that she made some movements and when he next awoke, about 4:30, she was dead. Was she poisoned by the drugs she was taking, because that's the only thing that medical examiners think of? They've got to find an answer for the death certificate. There are about four hundred thousand cases of sudden death in this country every year. About eighty-five percent of them are associated with obvious heart disease and there are some probably due to electrolyte disturbances. There are a few unexplainable cases and they're the ones that medical examiners go nuts over, trying to find what to put on the death certificate. The big problem is being able to tease out the small numbers that are due to drugs like thioridazine and mesoridazine. Fortunately, it hasn't been a major issue.

TB: While doing this research with psychotropic drugs, in the 1950s and 1960s, what was your position at the VA?

LH: From the time I joined the Veterans Administration, in the early 1950s, I was the Chief of Medicine, mainly at Menlo Park, California. It wasn't a very big position, because it was, primarily, a psychiatric hospital. But it was a rather odd title for somebody who, by the end of the 1950's, had become fairly well known in the field of psychopharmacology, to still be called Chief

of Medicine. In 1960, a new hospital was built on the Stanford campus, called the Veterans Administration Hospital in Palo Alto, a few miles away from Menlo Park. This was a Dean's Committee hospital, taken over by the faculty and staff of the University and I was really nobody, as far as they were concerned. They didn't know what to make of me, because I wasn't part of the official family. I was just on the clinical faculty. They had somebody else in mind for Chief of Medicine, so they made me Associate Chief of Staff for Research, which meant I was responsible for meeting the needs of a lot of prima donnas for research space. As you know, most of these hospitals are built with no research space and you have to create it. Fortunately, I was an old hand in the VA, and I knew how to get things done. Over the course of the first three years, during the 1960's, we created a lot of new research laboratories for faculty members, and that was one of my main responsibilities. By 1960, I guess the CINP had formed, but I never attended the meetings because I had a young family and didn't want to be traipsing all over Europe with them.

TB: When did you become a member of the CINP?

LH: Around 1960. About the same time I remember getting a call from Ted Rothman, in Los Angeles. I knew him as a clinical psychopharmacologist and he was in the process of starting a new society to be called the American College of Neuropsychopharmacology. Would I like to join as a founding member? I said, "Ted, there are so many societies these days, and they've just formed a new international one. Why do we need another one"? I tried to talk him out of even starting it. Finally I said, "Well, if you want to start it, I'll be happy to join as one of the first members." There were two meetings in Washington, neither of which I attended. It turns out, according to the by-laws, after two meetings you miss that are unexcused, you should be booted out! Finally, I went to the third meeting, which was also in Washington and punctuated by a blizzard that marooned us, but it was a good meeting. At the hotel, we were checking out, and Ted and his wife were nearby, so I went over and said, "You were absolutely right to found this society. It's a great one, I'm glad you asked me and I'm proud to be a member." From that point on, I don't think I ever missed a meeting.

TB: You became President of the College. When was that?

LH: I guess, in 1973. After that blizzard, we moved to warmer climates, most often to Puerto Rico, but also Phoenix, Las Vegas, and San Diego. We stayed away from snow.

TB: What about CINP meetings?

LH: I attended the first meeting, in 1964, in Birmingham, because my three oldest kids were old enough to travel and get something out of it. I got to know a lot of people in the CINP. One of the most impressive was Paul Janssen. I guess I was most impressed by Paul's facility with languages; like so many educated European scientists, he could switch from French to German to Belgian and English with no problem at all.

TB: So, you met Paul first in Birmingham?

LH: In Birmingham, and I considered him one of the few geniuses I have been privileged to know. He's a knowledgeable person.

TB: You, also, became the President of CINP.

LH: Well, later on, after a humble and reluctant beginning. I also met Phil Bradley, who was the host of the meeting, and later Phil came to do a sabbatical at Stanford, and I saw him periodically. I remember having lunch with Frank Ayd, who I've known since day one in the field. He was one of the first people I knew, and I knew of his sojourn in the Vatican, where he was an advisor to a couple of Popes. On Christmas 1962 or 1963, my secretary was going through the mail and said, "It looks like you got a Christmas card from the Vatican." I said, "That's undoubtedly from Frank Ayd, if it's not a signed picture of the Pope, I'll be disappointed." Well, it was just an ordinary religious Christmas card. Having lunch with Frank, I mentioned this story and Frank just kept a straight face. But, next Christmas, I got another card from the Vatican. This one had a photograph of Frank with twelve of his fourteen kids and the Pope. So he got one up on me, it really floored me. My second son probably still has that photograph somewhere. It was a nice time to get acquainted on a larger scale; I guess I'm fundamentally an organization man. Every organization I've belonged to, I wind up being active and becoming some official. I became President of the ACNP. At that time, there had only been one U.S. President of the CINP, and that was Paul Hoch, who was the second or third President. Since I was an authority with the ACNP, they figured I would be sort of a liaison as President of the CINP, and I was honored with that. I missed very few meetings of the CINP, one in Jerusalem and the one they had in Puerto Rico. Other than that, I've attended all the meetings. They, too, have been excellent.

TB: You were also involved with Jonathan Cole's Psychopharmacology Service Center.

LH: After the VA studies, in 1957 or 1958, the Psychopharmacology Service Center decided to do a study, and Jon asked me to be one of the members of the advisory committee. That's where I

first met Gerry Klerman, who was in the Public Health Service at the time. Gerry was a very impressive young man, had a lot of good ideas, and was a lot of fun to be around. Out of that came the nine-hospital Acute Schizophrenia Study, in which they recruited mainly from State hospitals. We also went to fancy places like the Payne-Whitney Clinic. In those days, there was much less consciousness of mania than there is today, and undoubtedly, all these patients were not really schizophrenic, but were probably acute mania and that may have altered the results somewhat. The study first proved that the antipsychotic drugs worked, which was no surprise. I'd always said that any idiot could tell, after you saw two or three patients, without any controls, that something was working. But, at that time, the ranks of psychiatry were very much against drugs, especially academic psychiatry, which was dominated by analysts, or analytically oriented faculty. That's why, in the history of these drugs, it's largely been the nonacademic centers that were involved, not the big academic centers. They thought this was all a fashionable thing. So, in order to persuade people there was really something to it, we had to do impeccable controlled studies to convince them this was not wishful thinking. We had to do what I call "massive scientific overkill." All these elegant controlled studies proved to the skeptics that there was something to it. Now this has become a routine affair. To get something through the FDA, you've got to do big controlled studies, similar to the early ones.

TB: Am I correct that you are saying these large multi-center studies were overkill?

LH: I think I can say this with no fear of having an axe to grind, because I was instrumental in getting that method going. Now we need to find new ways to prove these drugs that are simpler, cheaper and quicker, because to do these massive controlled studies, with a couple of hundred patients, costs tens of millions of dollars and takes about a couple of years to do. Furthermore, only people with big bucks can get into the field. If somebody has something that isn't patentable but it works very well, you have to overcome that. So, it's time to look for a different mode of operation.

TB: You got involved with Jon Cole's Early Clinical Drug Evaluation Units (ECDEU), as well?

LH: That's right. In fact, the government spent a lot of money establishing these ECDEUs, to do just that; to take flyers on drugs that might not have a big commercial backing and see whether they worked or not. That was a good idea, but it wasn't done in any systematic fashion. People did, more or less, what they wanted to.

TB: When did you get involved in the ECDEU network?

LH: When John Overall and I decided to split from the major VA studies and do these collaborative studies with maybe five clinics working together; we obtained one of the ECDEU grants to support that. And we went through a number of drugs and studies. We did a reprise on something I'd done earlier on chlordiazepoxide (Librium), studying possible withdrawal reactions. Around 1959, Roche was beginning to develop Librium. I had not studied it, but I was invited to a meeting in Princeton with the investigators, who had, and they were so uniform in their praise of the drug and all the patients swore by it. I said to myself, "If it's as good as they say, it's going to be abused." I previously mentioned I'd done a study with large doses of meprobamate in schizophrenics, so I thought I'd try similar large doses of Librium to not only study what it does in schizophrenia, but also, test the withdrawal reaction. I devised a study where we gave up to six hundred milligrams of Librium a day, after which most patients were ataxic, and then, very carefully withdrew them under controlled circumstances, measuring all kinds of typical criteria, including EEG's and plasma concentration. Unlike the other shorter acting drugs we had previously studied, the withdrawal reactions to Librium were delayed. The first couple of days, not much happened. By the third day, people began to get jittery, and by the fifth day, they had a withdrawal reaction, which was gone by the seventh or eighth day. From the plasma concentrations, we calculated the half-life to be about forty-eight hours. As a result, we described a new attenuated kind of withdrawal reaction, based on a longer half-life. Later on, that was done in our collaborative studies with diazepam, by one of the clinics without telling me, raising everybody to a hundred and twenty milligrams of Valium a day, and suddenly withdrawing them to produce the same kind of reaction. The fundamental conclusion derived from this was that the onset and severity of the withdrawal reaction is a function of the half-life of the drug. We studied another, meprobamate-like drug with a half-life of two hours but couldn't get anyone dependent on it.

TB: Was that drug, Tybamate?

LH: It was. With phenobarbital, which had been used for many years in chronically epileptic patients, there had never been any withdrawal problems, because with a ninety-six hour half-life, it has its' own tapering off action. That principle, we derived from different half-life studies, has remained constant ever since, and is still valid.

TB: Your idea of why there were no withdrawal effects with tybamate was rather novel.

LH: I think it was new. The whole idea of measuring blood levels, most of the drugs were new and the technology had improved. As the more complex drugs became available and more sophisticated methods were needed, this became a new area. In the 1960's, measuring plasma concentrations became fashionable.

TB: I think you were also involved in testing some of the biochemical hypotheses in psychiatry.

LH: Let's put it this way, I've always been a dilettante, and I've had the freedom to choose whatever I wanted to say. That's probably also been something of a disadvantage, because it hasn't kept me following a solid line of evidence, where I could develop a field entirely, but it has been interesting because I can go where I desire. Now, a number of things have come up from time to time that had theoretical implications in schizophrenia. For instance, one of the earliest was the pink spot. This was found only in schizophrenics, it was said, and chemically, it turned out to be 3,4-dimethoxyphenylethylamine, DMPEA. The dimethoxyphenyl group removed from mescaline. So, it was extremely interesting to think this might be the endogenous psychotogen that everybody was looking for, the chemical that caused schizophrenia. This had been postulated by Hoffer, Osborn, and Smithies about adrenochrome and various other substances. I heard that Arnold Friedhoff was playing around with it; so, I decided to see what it did in man and took the first dose, which was rather small and nothing happened. We gradually increased the dose, until it was obvious the compound had no activity, or so little, that it didn't matter. In the meantime, Arnold had been working on it in the military and found it was very quickly metabolized with a half-life, measured in minutes. So, we published two papers, one on the metabolism, and one on the clinical aspects. That scotched that idea. Another notion was that, if the dopamine hypothesis was correct, too much dopaminergic activity might cause schizophrenia. Things, other than blocking the receptors with drugs, might have an antipsychotic effect and, to this end, we studied a drug called acetyl methyl tyrosine, which has a specific effect on tyrosine hydroxylase, the main synthetic enzyme for dopamine. Sam Gershon and I were simultaneously beginning work on it but didn't get very far before they said we couldn't use it in man because in dogs it produced kidney stones. It turns out dogs have a very acidic urine and this material would normally be precipitated. So, it wasn't likely to cause any trouble in man, but we had to stop. We published our

results showing it had no clinical effect at all. Those were a couple of approaches to theories on what might cause schizophrenia.

TB: By that time you were also interested in chemically induced psychosis, right?

LH: That happened around 1960. I looked over the field with LSD and wasn't keen about the work that had been done so far and thought I could do better. My first question with any drug is to find out what it does clinically. So, I took pains to elucidate the clinical syndrome that LSD produced. Up to that time, you could read a hundred papers on LSD and not know what it did in man. Other hallucinogenic drugs were coming, including psilocybin and mescaline, which was an old hand. It turned out all three were almost interchangeable, except for there was a difference in dose, with mescaline being the least potent and LSD the most. Otherwise, they were all qualitatively pretty much the same. One of the interesting questions was whether LSD produces a model psychosis similar to schizophrenia. The idea was to get some tapes from people on the drugs and compare the interviews with schizophrenics. Painstakingly, we edited the tapes for any references that might tip off which tapes were which. Then we asked about twenty psychiatrists to review them, and all of them could tell immediately which tape was from the subjects on LSD and which the schizophrenic patients were. Then we said, let's see if psychologists can tell. They could. Then, let's see if nurses can tell. They could. Then, let's see if social workers can do it. They could. So it was obvious there were major differences in what the subjects were experiencing and expressing. That killed the idea that LSD produced an honest to God model psychosis. I used to quibble about that with Danny Freedman, who was interested in LSD from way back, and did similar work with LSD. We settled it by saying it might help in the very early stage of schizophrenia, but not with the later stage with the patients I studied. I still think I was right, but Danny was such a gentleman, you couldn't disagree with him with much enthusiasm. He was a fine, fine man. We did a lot of studies over the next 6 years, from about 1960 to about 1966, where we looked at LSD in facilitating psychotherapy, which was one of the major claims. We used LSD, psilocybin, and mescaline in various doses, taking patients who were stabilized in psychotherapy, and doing one interview with no drug, one with placebo, and one with each of the three drugs. So we had five interviews and I had a blind rater evaluate the interview content for how much useful information, psychotherapeutically, might have been derived from it. It turned out they were the same, and I concluded that, if you wanted to loosen up a patient for psychotherapy, a couple of

martinis would probably give you much more reliable data, because LSD, psilocybin, and mescaline muck things up. So, that was one of our studies. Another study was derived from the fact that some engineer, who had become a quack in this field, was going around the country and giving alcoholics 600 microgram doses of LSD, which is a fairly good jolt, with the claim that after one dose you were cured. You got instant insight into everything that caused you to be an alcoholic. That seemed to be too good to be true, so we tried to do a control study; I thought the best control drug would be dextroamphetamine. I took the first dose of 60 milligrams, and if I hadn't known what I'd taken, I would have thought it was the world's best tranquilizer. Everything was working on all cylinders in perfect tune, and it was wonderful. I couldn't sleep, but who cared? So, we used that dose as the placebo and then gave them a substantial dose of LSD. We found there was no good alcohol rating scale. At that time, everything was, either you're a drinker or you're not. I thought that was a rather foolish criterion, especially when you're trying to do a quantitative comparison. So, I got some psychological help to devise a drinking behavior inventory, which touched on the amount that people drank, the effect on their personal life, their job, and all areas likely to be affected by alcohol. It looked pretty valid and was able to make distinctions, but on further analysis, the major criterion for making these distinctions was how much you drank.

Simply tabulating the number of drinks per day would probably have been as good. About ten years later, somebody rediscovered the scale, and I began to get inquiries about reprints, but I never thought it was wonderful and I still don't think there are scales that quantitatively measure how much damage alcohol is doing. Not that I'm a convert to the idea of controlled drinking, which is very controversial, but since people are not generally going to be pro-abstinence, at least not most of them in treatment, getting them to reduce their drinking might be of value. We did every study we could with LSD, and by 1966, I decided to give up on it.

TB: Weren't you also involved with STP and THC?

LH: In the summer of 1967 in San Francisco, where all the hippies were born, there was a drug on the street called STP, which the Feds were quickly able to identify as 2,3dimethoxyamphetamine. I was at a meeting in Washington on drug abuse reform and a chap who worked for them, named Milt Jaffe, told me about the problem in San Francisco with this drug; they didn't know what was going on with it. He had some in his desk drawer and gave me

an armload of it. In no time at all, we found out it was identical, qualitatively, to the LSD, mescaline, psilocybin group. But, unlike them, tolerance developed fairly rapidly to repeated doses, and you couldn't block the effects with chlorpromazine or antipsychotics; the notion being that if these drugs were truly models of schizophrenia, then antipsychotic drugs should help. But they don't, they tend to make things worse. We had that all wrapped up and I sent a report within about 3 or 4 weeks to the Committee on Problems of Drug Dependence. They had a meeting to consider this problem, and the person who chaired it, the dean of drugs of abuse, was Nathan Eddy. Nathan was very impressed by the report and there was nothing to do but to become a member of the committee, which began a long association with that group. At that time, it was under the auspices of NASNRC and we met in their building on Constitution Avenue. In a couple of years, I became the Chairman of the committee, and served for several years, until the NAS wanted to reduce the number of committees and decided to "off load" this one. So, it became my duty as Chairman to shepherd the committee from the NASNRC to an independent state. It took a lot of time and effort, but it was worth it, because the committee survives as a College on Problems of Drug Dependence, a membership organization and the most prominent, scientifically impeccable group, devoted to substance abuse. About 1966, Mechoulam in Israel finally determined the true structure of THC, which was not much different from the structure of the compound synhexl, discovered by Adams in England around 1940.

When THC became available, I decided it would be interesting to study the clinical effects, and to know if synhexl was like THC, because synhexl had been used in a lot of clinical studies for possible therapeutic uses. At that time, there was a retired pharmacologist from Abbott, R. K. Richards, working in our area, who went back to Abbott and was able to get some twenty five year old synhexl in a little glass vial that was in the freezer. It looked like a bunch of tar, but we reconstituted it in alcohol and water, and were able to make a hydro-alcohol solution, where we knew the dose and compared it with oral doses of THC. So the first study was a comparison between synhexl and THC. To make a long story short, they were very similar, the major differences being synhexl had longer latent periods and it was weaker. Otherwise, it was qualitatively quite similar, which gave validity to the previous work that had been done with synhexl. We were also able to develop the clinical effect and time course of THC on neuron intoxication, and I plotted this on a time scale, graphically. Two or three years later, when labeled

THC became available, Lemberger in Axelrod's laboratory did the same study using labeled material, and it was the same one we drew from clinical observation.

TB: When did labeled THC become available?

LH: Around 1965 or 1966. Harris Isbell and his colleagues in Lexington had it first, and we were the second. A chap named Andy Weil got into the game at that time. He'd just graduated from Harvard Medical School, and he'd been a botany major as an undergraduate. So he was interested in drugs in plants and embarked on a study using marijuana. His paper was published in *Science*, but I wasn't bright enough to figure that this would be of interest to *Science*, so I published my results in the clinical pharmacology journal. I must say, in all fairness and not being modest, our paper was more informative than his. Andy became propelled, all of a sudden, into the first ranks of substance abuse people, about which he knew nothing. When it came time for him to go into the military, he wanted to go to the Public Health Service, and they offered to send him to Lexington. Anybody in their right mind, who wants to do things in substance abuse, goes to Lexington to learn the ropes, that's the Mecca. But, Andy turned them down. At one meeting, Andy was giving his paper and I was sitting next to Jerry Jaffe, who looked over at me and said, "Is this guy for real?" I replied, "You said it, Jerry, I didn't." So I'm not at all surprised he's currently the big guru of alternative medicine and probably making millions of dollars, but as a scientist, he was zilch. You do run into some strange people. Anyway, that got us started on studies with marijuana, which continued until recently. I don't think we've done anything for 3 or 4 years, but I've a couple of studies still not written up for publication, and we covered, pretty much, all the aspects of marijuana.

TB: Could you review the most important steps in that research?

LH: I can't think of all of them. We did electrophysiological studies, things like contingent negative variation and continual EKG recording. We studied the biochemical effects vs. clinical effects, over and over, using the various isomers and found out that cannabidiol and cannabinol, the only other naturally occurring cannabinoids, were virtually clinically inactive and there was no interaction between them and THC. We studied a number of other interactions with THC. It was a sizeable body of clinical work and probably the largest on THC and marijuana that's around.

TB: What were your conclusions?

LH: If you got a big jolt of it, you get a very rapid heart rate and conjunctivitis, both of which we showed were accurate in determining how long the drug was effective. The tachycardia can be a problem in people with angina, but on the whole it was very safe.

TB: Do you think it should have a place in treatment?

LH: We came to the conclusion that there are very few contraindications to using it. The evidence is shaky, but our clinical evidence suggests that if you have a history of schizophrenia or mental illness in the family, stay away from the drug. The Swedish experience suggested that there's a more direct relationship, but I'm not sure. We did notice when patients would go on week end passes at our hospital, they would often come back on Monday kind of loony, and if we did urine analyses, we'd find they had marijuana metabolites in their urine. This led to a routine practice of checking people when they came back from passes. Most of them, who had positive urines, also had some clinical deterioration. So, I don't think it's good for people with mental illnesses, or for people with coronary disease, to have it. Probably among social drugs, it's as safe as any, but maybe caffeine is a little safer. I don't know. It doesn't cause anywhere near the morbidity and mortality that nicotine, in the form of tobacco, does and certainly not as much as alcohol in its various forms. As far as therapeutic uses are concerned, the case is already made that oral THC can be effective to treat nausea and vomiting associated with cancer chemotherapy. It's on the market and rescheduled as Class 2 for that indication. The only trouble is, the company who makes this stuff and who got a totally free ride from NIDA in developing it, charges an arm and a leg. It's very, very expensive. If you do the same thing with marijuana cigarettes and buy them on the street corner, you could save a lot of money. There's no reason, pharmacologically, to believe that if the oral preparation works, the slow smoked preparation shouldn't work. It would be on a different time schedule, because the pharmacokinetics is different and we explored it extensively. The other possible indication is the relief of pain; nobody has any idea of how it does that, but there are enough reports that it has some analgesic effect. I rather expect that's going to await the development of the synthetic cannabinoid, which may not have the mental effects, and which could be patented in analgesia.

There's also some reason to believe that it's effective against muscle spasticity, which is not very well relieved by any existing drug. That has hardly had any work and deserves much

more. So, there are some valid medical indications that need more exploration and I don't see any reason to think that marijuana is any different from any other drug being developed.

TB: Have you published on that?

LH: The final draft is being typed up this week and will go off to Israel next week.

TB: To the CINP journal?

LH: Sure. It probably has 200 people submitting important papers, so it might help the new journal get off the ground, and secondly, they give a good review. I may not agree with all the referees, but I don't mind telling them when I don't, and when I do, I am very grateful.

TB: That's the last paper you wrote. Am I correct?

LH: I don't know whether I'm going to write any more or not.

TB: Well, let's just see.

LH: As you get older, you do less original research and more review papers. I've got a paper coming out in the *Canadian Journal of Psychiatry* on "Calcium Channel Blockers in Psychiatry." We did a study on that a few years back, which seemed to indicate that Verapamil was about equivalent to Lithium.

TB: You started to work with calcium channel blockers years ago?

LH: I think our study was published about ten years ago and there were weaknesses in it. First of all, the sample size was small, and you had a very good chance of not being able to reject the null hypothesis. The second thing was, I don't know what was wrong with our patients, but none of them did very well and the results of the treatments were rather poor. But the *American Psychiatric Journal* accepted it and there were a few other reports that suggested it might be useful, including a number of papers on mania, going all the way back to the early 1980's. A fellow named Dubosky, in Denver has done most of the work. Curiously enough, there's a whole chapter on this in the new textbooks that the APA published. There have been two studies, one from Australia that indicates it wasn't nearly as good as lithium, and the other one, from John Davis' group, saying that it was ineffective compared with placebo. Now, if that doesn't kill it, I don't know what does.

TB: Let me just switch a little bit. When did you start to work with lithium?

LH: I never did much work with lithium.

TB: Why was that?

LH: Being an internist gave me a disadvantage, because I remember in the late 1940's, lithium chloride was introduced as a substitute for sodium chloride in patients with congestive heart failure. The idea was, you reduce the intake of sodium, but all of a sudden, a number of these people died and it was probably lithium toxicity, because due to the diuretics they were also taking, they weren't getting rid of it. So, when I first heard of lithium in psychiatry, I said that's a poison. I couldn't imagine it could be useful. I think Sam Gershon did more than anybody, along with Cade's work in Australia, to popularize it in this country. I regret I had very little to do with lithium, because it certainly was one of the major advances.

TB: Let's go back to the 1960's. Some of the theories about the mechanism of neuroleptics came about, in 1963, via the dopamine theory of Carlsson and Lindquist. You worked with haloperidol, at first, in the early 1960's, and with some of the other buspirones. Is there anything you'd like to comment on in the treatment of schizophrenia?

LH: Recently, I had occasion to look at a paper I published, in 1962, which I think was the first North American paper on haloperidol, and I was dumbfounded. The doses we used to produce an antipsychotic effect were two to four milligrams a day. I thought, oh my God, I forgot my own lesson, because I'd been using ten milligrams and had some people on massive doses, and we've all been using too damn much. It's interesting to think, in terms of the atypical antipsychotics, that if we compared them to four milligrams of haloperidol, instead of ten to fifteen, that the differences would not be so great in terms of extrapyramidal reactions or tardive dyskinesia, but we missed the boat. There were a couple of people in New York, one of them named Haase, who developed a dosage threshold, the onset of micrographia.

TB: That's right.

LH: They showed you could get detectable micrographia beginning at very low doses as a neuroleptic threshold, but I didn't believe it. They were right. We've been using, altogether, too much.

TB: Paul Janssen was very much for the handwriting test. In the late 1960's, he was so much in favor that one should use it, that he published a book, "Neuroleptic Drugs," written, a very small part by Janssen, the rest by Haase. So there was some kind of disagreement between the real clinical needs and marketing.

LH: I remember Paul telling me that the custom in Belgium was to have it in liquid form and let the nurses regulate the dose, drop by drop, literally. They were using low doses and very small increments, but we all missed that. If we did a new study comparing the atypicals with small doses of haloperidol, it might not look as different as people think.

TB: Did you work with the atypicals?

LH: No, I've not worked with any. By that time, I'd long since given up testing drugs. Back when John Overall and I were working, and nobody knew what the best ways were to give the drugs, what was the best way to use rating scales, or what were the best statistical procedures, it was something you could contribute that was original and scientific. Now, it's all become so standardized, the drug companies have big groups of people designing protocols, rating scales and report forms, and analyzing statistics. They come to an investigator with a protocol about that thick, all written up, including the consent form, and if you say you'll do it, they ask how much? I saw a protocol the other day for fourteen patients and it cost about \$140,000.00. It reduces the investigator to a mere peanut gallery, and most of the studies are done by the flunkies they hire, so there's no scientific input at all. Will they accept the investigator's article? No, they send it out to some flack firm that specializes in writing papers and it is written impeccably by people who know nothing about the study. The names on the paper go by how many patients you've contributed. Well, that's a helluva way to do things! I can't think of anything duller. So, I gave it up years back. The last study I contracted to do, I did only to get one of our new faculty started.

TB: So, you think we are missing the boat by having a bunch of people design something, then someone else generates the data and processes it.

LH: My feeling is that any time things get standardized, that's an excuse for not thinking.

When things become routine and standard, that means you stop thinking. All the protocols now are impeccable and they sail right through the FDA. The FDA loves it, so all the companies want to do is get one or two of these multi-clinic studies.

TB: Do you think that any of these atypical neuroleptics might not be different if you look at some of the old drugs with receptor assays? Do any of these new drugs contribute anything major?

LH: That's a big issue right now. I was recently at a meeting convened by a group of mental health and mental retardation administrators and they're getting terrible pressure to purchase these new second generation atypical antipsychotics for all of their schizophrenic patients, which would

break their budgets. They wouldn't have anything left for anything else, because these things cost up to a hundred times as much as haloperidol. I don't think anybody realizes how terribly expensive they are and how cheap haloperidol is. Ten milligram tablets of generic drugs probably cost less than ten cents. You're talking pennies versus dollars. So, there's a big drive to petition the State legislature to appropriate fifty million dollars, or whatever, to buy atypicals for more patients and citizens' groups are demonstrating at the Capitol. Some of the people from NAMI and other advocacy organizations are claiming this is a magnificent new era of psychotherapeutic drugs, we are doing patients an injustice, and it would be unethical not to treat them with these drugs. Now, you know where that orchestration is coming from. It's very well organized by the drug companies, because they would like nothing more than to have these drugs declared first line treatments. I don't agree with that and I tried to point out the difference, so people don't get misled. If you had unlimited amounts of money, then sure, treat everybody with a drug that costs several dollars a day. What difference does it make if somebody else is paying for it? But if I had to pay for it, out of my own pocket, I might have a little perspective.

TB: You are still of the same mind as when you wrote a book with Ole Rafaelsen, *Mini Psychopharmacology*. When was it?

LH: Sometime during the 1970's. It was Ole's idea and became enormously popular. He thought of it as guide for developing countries and I forget how many languages it was in.

TB: At least ten or twelve.

LH: I didn't think it was going to be so popular, but it was essential information, which even the barefoot doctors in China could use and it was probably translated into Chinese.

TB: I think it was. If my recollection is correct, you said in that book, chlorpromazine and haloperidol are the two drugs you can do everything with. So you would still say that, right?

LH: I don't work in the field of basic receptors; but the only difference between the atypicals and the older conventional drugs, if you look at the receptor profiles, is that common to every atypical is a weak blocking action on D₂ receptors, while serotonin blockade is variable.

Besides, there's no way of proving that serotonin blockade has a damn thing to do with extrapyramidal reactions or schizophrenia. Tensin, which is probably the best available 5HT₂ receptor blocker, has no effect, or Janssen would be selling it. Nobody knows what D₁ blockade does while D₃ and D₄ are the same story. I was talking to somebody recently, who said there's a

current study going on with a D_{2A} receptor blocker, showing an antipsychotic effect. If that is the case, there might give some truth to the idea, but, so far, I don't think there's any evidence. The new drugs work exactly the same as the old ones, only less.

TB: What makes olanzapine and risperidone so successful then?

LH: Joe Siegleman claims that is due to the fact they do not bind as tightly to a receptor as the conventional drugs and are easily disassociated, so they're in and out. But if this occurs, why should they not also produce extrapyramidal reactions as well as antipsychotic effects? Well, he thinks it has to do with the rate of firing, with the extrapyramidal dopamine receptors firing more rapidly than the others. That may be the explanation. Of course, if you look at the evidence that's accumulating, all of them will produce extrapyramidal reactions. It's simply a matter of dose. I don't see what is so monumentally different from what we had before. Now, what could be the effect of a weak D₂ receptor antagonist? It could reduce extrapyramidal reactions, especially when you're comparing it with fifteen milligrams of haloperidol. It could in turn, allow these extrapyramidal reactions to be mistaken for negative symptoms, apathy, and so on. That may explain the atypicals so called superiority in treating negative symptoms, which may be more apparent than real. It could also be because some of them don't seem to have a whole lot of sedative effects; although clozapine and olanzapine have plenty. It could account for the improved cognition, which I think is minimal anyway. So, if patients are less impaired by extrapyramidal reactions or sedation, it may contribute to social rehabilitation. But, these speculations are not proven. They're just possibilities and I think we're buying a lot of expense we don't need.

TB: You are more or less saying that not only are we buying a lot, but, even with the old drugs, we are overdosing. Forget about the new drugs, because there is not sufficient evidence they are different, but are you saying that with drugs like haloperidol, we should get back to the old handwriting test or something like that, and use lower doses?

LH: I would be tempted to start every day on a very small dose of haloperidol and use the classic tests to determine the neuroleptic threshold. If, at that time, the psychosis hadn't responded, using diazepam to control the behavior, then, perhaps, add a very small dose of one of the newer drugs to increase the blockade, but not crossing the neuroleptic threshold. That would save us an enormous amount and reduce use of the new drugs and pair them with older drugs where they might have some effect. Let's just say it's theoretical. I don't know of anybody who's doing this.

TB: What you are saying is understandable and I agree with you. Let's stick with that topic, because you and John Overall were not psychiatrists, but were among the first who tried to tease out which patients were responding. Am I correct?

LH: To find the right drug for the right patient has been a very frustrating experience. John and I tried it. Jim Clavin and some others in the VA tried it, and we all seemed to come to conclusion.

TB: Would it not be possible that responders remain hidden because of the measurement instruments you employed?

LH: It may be that the questions you ask determine the answers you get, and when you use these instruments all you are doing is codifying the mental status examination, and the questions determine what areas of psychopathology you learn about. It may be that kind of clinical approach is past and we ought to think in terms of biological outcomes.

TB: Are you sure we might not benefit if we would get better clinical feedback compared to this receptor kind of thing?

LH: I wouldn't want to knock anything clinical. I'm a hundred percent for that.

TB: I'd be surprised if you weren't.

LH: You can learn a lot by talking to patients, looking at them, and observing. I've never been impressed by these elegant studies of behavioral pharmacologists on drugs of abuse, where they show that a drug abused on the street is self-administered by monkeys. You'd have to be an idiot to think it wasn't. So I keep wondering are we doing things the hard way, rather than taking a simpler and more direct approach. Of course, the simple things don't look so scientific. If you get self-administration diagrams, that's science, compared to if you can show that people, given a chance, self-administer the drug.

TB: Let's push that in a slightly different direction. With atypical antipsychotics, the very first papers were not in schizophrenia. The effect moved to schizophrenia when something had to be verified in a more homogeneous population, other than all psychotic patients combined. Everything is now depending on the assumption that we have a homogeneous category, a disease entity which was artificially constructed and a measuring instrument designed to show change in it. But if the disorder is biologically heterogeneous and our measures insensitive to these differences, how would we be able to demonstrate that drug responsiveness differs? It would be very difficult to tease out. Is that what you're saying?

LH: Yes. Of course, you have to look at it from an historical point of view. In 1955, the New York Academy of Scientists had their second meeting on reserpine, which was all on schizophrenia. They had everybody who was using the drugs, or almost everybody, including Nate and me. Not a paper in that whole bunch told what kind of psychiatric patients they were treating. Mine was the only one that tried to use the DSM II, I think it was.

TB: It was DSM II.

LH: My studies were blind and controlled, and that captured the attention of the press. We tried to grade the improvements clinically, but no instruments were used. The attraction to my paper caused them to feature it on the news wire, and in a day or two, every newspaper in the country had an article about the new drug for schizophrenia with me as the principal investigator.

A couple of days later, the mail started in from all over the country. I've got a son; I've got a daughter; I've got a husband; I've got a wife who is schizophrenic. Nothing is helping; can I bring them to get this new treatment? It took a lot of time to answer every one of them personally, but it was impressive to see the power of the press, and the anguish of people who had a relative with a catastrophic illness. Nate fully expected to go to that meeting and be the star, but I upstaged him! The Lasker award, at that time, was brand new. Mary Lasker had decided to honor her husband with the award and she was very interested to make the award for advances in the treatment of mental illness. When the award came out Heinz Lehman and DeLay got it.

TB: As well as Deniker and Laborit.

LH: And, Bob Noce. Nobody had heard of Noce before and nobody's heard of him since. He was just a State Hospital psychiatrist that Dick Roberson said would try our job. I was talking to David Healy and he said, "Why didn't you get the Lasker Award?" Then I realized I probably screwed myself out of it by upstaging Nate, because Mary Lasker listened to him. That does seem to be the only rational explanation of how Bob Noce, who was a nice simple minded guy, could wind up with a Lasker Award. I'm not even sure that Noce had any major publications.

TB: Let's discuss the antidepressants. Theorizing about the antidepressants starts, in 1962, with Axelrod and norepinephrine reuptake, and simultaneously, with the Brodie group. If my recollection is correct, you had a paper on desipramine.

LH: Desipramine, but we never saw a whole lot of results from it, because we used too small a dose.

TB: What was the dose?

LH: Between 75 and 150 mgs, and 100mgs is probably too small. I remember Brodie, who could be somewhat sarcastic; although we got along well, said if you want a drug to work, you've got to give it in the proper dose, and he was right. So, I never felt keen about that study; we don't hit homeruns every time we go to the plate. Sometimes we strike out.

TB: But independent of whether the dose was adequate or not, it triggered a development which moved things from the non-selective view of tricyclics all being similar. Was that warranted?

LH: At that time, I don't think there was much interest in trying to separate the norepinephrine depressions from the serotonin depressions. Desipramine is a selective norepinephrine blocker, but we had nothing that was selective for serotonin in those days. So, you couldn't test the hypothesis in a clean way; although, I'm sure many people, as well as myself, thought of it. Wouldn't it be nice to do the study? The closest I came to it was when I suggested that to some group, and Sandy Glassman said he took a crack at treating depressed patients initially, with desipramine, a norepinephrine blocker, and then the failures, with amitriptyline, which was the most serotonergic of the mixed drugs, to see if we could tease them out. But after they treated eight or ten patients, they all responded to desipramine, so they had no way to make the comparison, and they stopped the study. I don't even know whether they published it. There was no way until the selective serotonin uptake inhibitors came along to test the hypothesis, and I don't know anybody who did that. Do you know anybody that tested selective serotonin inhibitors vs. desipramine?

TB: There are isolated studies, which were in both directions, but you have to have a 60 percent response rate before the whole thing is meaningful. So it's very difficult. Do you have an opinion about whether there is anything to separating out the two groups? Do you think any major contribution has been made since imipramine in the antidepressant category?

LH: In my opinion, the most interesting and original antidepressant is not a serotonin uptake inhibitor, but bupropion (Wellbutrin).

TB: So, dopamine?

LH: Which, as far as we can tell, works on dopamine, but it's not clearly defined as to how. If you look at the molecule, it's the basic phenylethylamine structure, but they modified the side chain and this attenuated some of the amphetamine like effects. So when I see a patient and I think the

depression would be ideally treated with something like amphetamine, I prescribe Wellbutrin, and it works.

TB: Would that be a particular kind of depression? In the 1964 paper with John Overall, you had four different types of depression. Would one or another be more suitable for Wellbutrin?

LH: I don't use the subtypes characterized by that rating scale. I guess I could. One thing that came out of that was the tricyclics were effective for endogenous or what we called retarded depression.

TB: Are there any other useful sub-types of depression in terms of treatment?

LH: Deniker's group has classified a mixed anxiety depression syndrome. We called it anxious depression. We brought attention to that, which is beginning to become a very popular idea. People are beginning to think there is some sort of comorbidity, or maybe, anxiety is part of depression. I remember raising this question with a psychiatrist and he said, "I can imagine somebody being anxious and not being depressed, but I have trouble imagining somebody being depressed and not being anxious." I thought that was not a bad summary statement. So, more and more, you're getting overlaps, where panic disorder, for instance, is being treated with antidepressants, and sociophobia and some of the other anxiety syndromes have more overlap with clinical depression. Trying to separate these isn't valid and may be due to our desire to oversimplify.

TB: Is there any study to compare bupropion with a norepinephrine uptake inhibitor?

LH: I think it would be interesting to compare bupropion and reboxetine.

TB: But is there any?

LH: No.

TB: Do you think it should be done?

LH: From a theoretical point of view it would be very nice.

TB: And with dopamine agonists we are actually pushing more of the receptor activity approach?

LH: Bupropion also emphasized that it doesn't interfere with sexual function. That's a good selling point, with Viagra being so successful. Another drug that would have been very interesting, if it had lasted, was nomifensin.

TB: It died because of side effects.

LH: All the evidence accumulated before they stopped it was very clean. It must have broken their hearts to take that off the market.

TB: That was the first drug effective on the dopamine system. Now bupropion is side-tracked with another indication.

LH: I don't have any idea why it works in making people give up nicotine, but it apparently does.

TB: It looks like it. But you weren't as much interested in this norepinephrine and serotonin comparison?

LH: Many people use the response of imipramine to formulate the idea of serotonin in obsessive compulsive disorder, but they forget the metabolite is mainly acting on norepinephrine, so I didn't think that was a very clean example. But there are others now that link serotonin and obsessive compulsive disorder, like zimelidine.

TB: Arvid Carlson claims it was the first one. He keeps on telling people about tryptophan passing the blood brain barrier.

LH: I've never been very convinced that the precursors loading strategy is good evidence. First of all, tryptophan goes into the brain, but it doesn't know where to go, so it goes everywhere. You flood the brain with tryptophan and presumably increase serotonin everywhere, but that doesn't answer many questions and it could be there are places you don't want it to remain. We did try a precursor loading strategy with choline, trying to treat Huntington's chorea, tardive dyskinesia, and ultimately, Alzheimer's.

TB: The argument you used for neuroleptics, wouldn't that apply to antidepressants; you wouldn't feel there is a justification to buy the new expensive ones?

LH: One of the earliest meta-analyses was a comparison between serotonin uptake inhibitors, as a group, and the tricyclics taking all the published papers where there was some direct comparison. It was published in the *British Journal of Psychiatry* about 1994, and concluded, in terms of efficacy, there was no difference. In terms of side effects, it was a trade off with a marginal value for the selective serotonin uptake inhibitors, but in terms of people completing treatment, there was no difference.

TB: There is another meta-analysis, a very recent one, and they claim that there is no difference in side effects, as well.

LH: I've taken tricyclics and they're not pleasant. I also took fluoxetine (Prozac), twenty milligrams a day for about ten days, and I wouldn't have been sure I was taking anything. I was impressed by the fact there were hardly any discernable side effects, which was much different

from the tricyclic. If I had to have an antidepressant and was given a choice between a tricyclic and fluoxetine, I'd probably choose the newer one.

TB: In an advisory capacity to the State of Texas, would you suggest: if there is a major price difference, to use the newer drugs or would you say to stick with the cheapest?

LH: I'm in favor of the treatment where you get the most bang for your buck, and when the price differential is great as with the antipsychotics, I prefer the generic haloperidol, which is dirt cheap. With antidepressants, the differential is not so big. One of the things that seem to stand out is that the more disturbed you are, the more tolerant you are of side effects. Most normal people find antipsychotics to be intolerable and the same is true of antidepressants. When you're truly depressed, the side effects are more tolerable. It may be you could be justified using conventional drugs first, and if the patient becomes intolerant or non-responsive, switch to the newer ones. I figure you're going to get your money's worth if they are better tolerated and more effective. In everything in life, you have to make a judgment between cost and benefit. Since there seems to be a finite amount of money for treating psychiatric patients, I'm going to think a long time before I spend that money. When the patient says, "I feel a little better on one drug than I do on the other, well, that's tough." You're getting well. That's what counts. In the case of a local situation, if schizophrenic patients are admitted to the mental health authority and treated with the new drugs, there wouldn't be any budget left. Nothing for lodging, nothing for social rehabilitation, nothing for vocational assistance, all of the other services that patients need in order to function in life and stay out of the hospital, so if you're buying expensive drugs and have to give up all the rest of the treatment, that's a bad bargain. We have to view the situation broadly. Nobody thinks that drugs, alone, are going to answer the problem. The best we can do is make it possible to use other avenues to try to improve the lot of the patients, and if you can do that by allowing them to live or function in the community and do some sort of productive job, those are the outcomes by which we measure success. We don't have a lot of people who have been schizophrenic go back to being concert pianists. They may try, but it seldom works. So, you have to set your sights, as you would for any handicapped person, because if they have a physical handicap, you try to teach the patient how to work around it and do the best they can with the handicap. You don't think you're going to get rid of it, but you're going to try to work around it, and I think we have to do that with our impaired psychiatric patients.

TB: You became interested again in choline, so, could elaborate on how you have contributed?

LH: We didn't have anything to do with the development of it. That came from Peter Whitehouse and his colleagues where they traced these cholinergic tracks in the brain and showed there was some relationship between them and Alzheimer's. There was indirect evidence suggesting a cholinergic hypothesis, and I and Kenneth Davis, got very interested in this. I had run across an abstract in Federation Proceedings by the guy at MIT who worked with Axelrod, in which they indicated you could use choline as a precursor for acetylcholine in the brain. Again, we flooded the whole brain. It turned out not to be very practical, because when we started using it on patients, the ward smelled like an old fish market; the choline changed to trimethylamine and that is what makes dead fish smell. We tried a number of cosmetic devices to try to deal with that but had the impression we were losing the nursing staff, so we stopped it. Lecithin has to be metabolized in the body to free choline and it made much more sense. We also tried physostigmine and replicated studies Dave Janowsky had done with it in mental patients, and that too, caused a rather dramatic change. One of our manic patients, as we were doing the physostigmine infusion, suddenly became very depressed, starting crying, felt awful, and we had to stop. That was a rather dramatic change of mood which suggested acetylcholine might play a role in the switch process, which has never been fully elucidated. Most people think it's due to dopamine. In tardive dyskinesia, with the physostigmine infusion, we could show by videotaping them and blind ratings, there were substantial changes in abnormal movements, but they are extremely difficult to show because they're so variable anyway.

TB: Anything else in Alzheimer's? You worked with Hydergine at the very beginning and did you work with any of the nootropics?

LH: No, but I was first with Metrazol and Hydergine. We did one study where we used six milligrams a day versus three milligrams of Hydergine and got a little result. There was a question of the basis of response, but we couldn't take the dose higher because it was rather expensive.

TB: You have contributed to many, many areas in psychopharmacology. What would you think was your most important contribution?

LH: I feel somewhat disappointed I can't point to a single real discovery in the sense of something vastly new or revolutionary. I attribute it partly to my free will, to the freedom I've been given to follow wherever I want to go, which tends to make you more diffuse compared to somebody who

says I'm going to focus on one thing and find the answer. If I had it to do over again, I'd be more focused.

TB: But you kept things close to real, to Mother Earth, all through, because you kept on reevaluating and trying to establish where we really are. You contributed an awful lot just reviewing the whole field. You did that with great regularity. Am I correct?

LH: Yes, I think one of the contributions you can make is to try to reduce data into something understandable and coherent. I had a good ability to do that. As far as the experimental contributions are concerned, I would say the most important, probably, was the introduction of controlled clinical trials in psychiatry, which is still a major influence. It would have happened without me, but I think I gave it a little push.

TB: A start. You were the first.

LH: The first. The second thing might have been the ability to look at drugs beyond the psychiatric, to their general medical effects, including the complications of the use, which I don't think a whole lot of people in the field were able to do.

TB: You wrote several books and some of them had several editions. I think one of them is just getting into the fourth edition, right?

LH: Just three editions; *Clinical Pharmacology and Psychotherapeutics*. The co-author was one of my brightest protégés, John Samanski, who's now one of the Washington University faculty, but I don't think he's very anxious to do a fourth edition. I suggested we try to do a 3rd edition, focusing on what might be called Evidence-Based Therapy, but although it's a catchy approach, I don't think it's all that good.

TB: Was the book translated into any other languages?

LH: No, the publishing house doesn't seem to have much zip.

TB: So the book which is in all kinds of languages is with Ole, right — *The Little Book*?

LH: Yes, Ole and I never made a penny off that book, but that wasn't the goal, and it served the purpose Ole had in mind. Ole was a truly remarkable person. I remember the first time I went in, someone had referred him to me, and I said, "Come on over to the hospital" and he replied, "I'd like to see what's going on in the research area." So, at that time, I was Associate Chief of Staff for Research and knew all the research going on, so I took him everywhere, neurology, cardiology, psychiatry, and surgery. Within one minute, he could be talking intelligently to the person

describing their research. I never ran into anyone who had such a broad based knowledge of medicine as Ole. He knew what was going on.

TB: He was involved in research in diabetes, right?

LH: Yes, I visited his outfit in Copenhagen and he had several things going, but some of them were not psychiatric. He, also, had been trained in medicine first; although he did have some formal training in psychiatry, which I never bothered to get. But, I had the utmost respect for him and he was a delightful person. One of his unknown accomplishments was a book of erotic limericks of his own composition. He was just a wonderful person.

TB: We have a few more minutes to talk about a couple of people you collaborated with, or who you would like to mention.

LH: The former president of the CINP is always supposed to have some say in who follows him, but you were kind enough to ask me several times after my term ended. The first person I wanted was Arvid Carlsson, and we got him. The next person I wanted was my other idol, Paul Janssen, and we also got him. Finally I got Ole, after Pual Kielhotz and Biff Bunney. When Ole took over, it was only two or three years later he had the tragic accident that killed him. If he had lived, he would have been a big figure.

TB: Leo, thank you very much. I think we used up our time. I really appreciate your contribution. It was very enjoyable.

LH: Well, you've been enjoyable, too.

31. PHILIP S. HOLZMAN

TB: This will be an interview with Dr. Philip Holzman³³ for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College in San Juan, Puerto Rico. It is December 9, 2002. I am Thomas Ban. Let's start from the very beginning; when and where were you born? Tell us something about your childhood, education, and move on in chronology.

PH: I was born in New York City, on May 2, 1922. My father was an accountant, and my mother was a painter who loved Millet and would spend time in the Metropolitan Museum of Art copying his art. She loved the peasant scenes he drew so beautifully and poignantly. My mother died when I was 22 months old. I was reared by my mother's parents, in New York City. My father remarried about two years after my mother's death and chose to have me stay with my grandparents. So, essentially, I was reared by older parents and have never ceased to have a fondness for older people. I went to public schools in New York. My high school was Townsend Harris High School, at 23rd Street and Lexington Avenue, to which I had to travel on what they then called the Interborough Rapid Transit, the IRT. It was about a 25-minute ride that gave me time to do the homework I had not completed the night before or to read either the *Herald Tribune* or the *New York Times*, which one could buy on the news stand for 3 cents.

After graduation from high school, I went to the College of the City of New York and didn't have the foggiest idea what I wanted to do. One summer evening in 1939, it must have been about a month before Sigmund Freud died, I heard a heated discussion between two people in their early 20s. It was about Freud and psychoanalysis. I couldn't understand what they were talking about. The arguments that I used to hear in my high school and in the college cafeteria had to do with collective security versus isolationism, with Stalinists versus Trotskyites that left me rather cold. I could not quite get involved in that. But this argument somehow intrigued me because words floated by such as dreams, the unconscious, instincts, and sexuality. My goodness,

³³ Philip S. Holzman was born in New York City, New York in 1922. He received his Ph.D. from the University of Kansas in Lawrence, Kansas, while working at the Meninger Foundation, in Topeka, Kansas. He was, then, recruited to join the faculty of the Department of Psychiatry at the University of Chicago in Chicago, Illinois. He joined the Faculty of Arts and Sciences at Harvard University and the Department of Psychiatry at Harvard Medical School and McLean Hospital in Belmont, Massachusetts. Dr. Holzman died in 2004. He was interviewed at San Juan, Puerto Rico on December 9, 2002.

sexuality! You know, for someone who was in the late teens at that time, this was very seductive. After hearing that argument, I went to a bookstore and bought a copy of A.A. Brill's translation of several papers of Sigmund Freud. It included the "Three Contributions to the Theory of Sex" and "The Interpretation of Dreams," but when I started to read them, I was more bewildered than before. I later understood that A.A. Brill, while a passionate acolyte of Sigmund Freud, did not know either German or English well. His language was Yiddish. So he used an amalgam of languages.

Psychoanalysis didn't capture my interest until my second year in college, when I took my first course in psychology. My instructor was a man named J.E. Barmack, who had us read a number of wonderful works, such as Kleinberg's *Race Differences*, and the *Introductory Lectures to Psychoanalysis* by Sigmund Freud, translated by Joan Riviere, who certainly knew English. And this was quite revealing. I found that Freud was a master expositor and was totally taken in by his arguments in this interesting psychological discourse of what the inner life is presumably all about. So, I resolved to study psychology, and I majored in it. Before that, I didn't know what I wanted to major in. At the time, I wanted to be a journalist but I quickly changed course. And the odd thing is that what captured me was experimental psychology. I took two courses in experimental psychology, one in physiological psychology. I was captivated by the idea that by experiments, you could tease apart one variable from another in mental life. This was a revelation to me because Freud was an expositor; he laid out "This is the way it is," while in experimental work we ask, "Is this the way it is?" I thought, "That's the way I would like to go." Then I was inducted into the army. It was World War II.

TB: So we are in the early 1940s?

PH: This was 1943. The United States had been in the war since the end of 1941, December 7th, and that was the end of my education up to that point.

TB: So you studied psychology and physiological psychology?

PH: Yes.

TB: Did you graduate by then?

PH: I had a bachelor's degree, but no more. I was in the army for a bit over three years and discharged in late August of 1946. I was in the Pacific and ready to invade Japan, if it had come to that. Since I didn't know what I was going to do after my discharge, I wrote to a professor,

Gardner Murphy, who had been the chairman of the department of psychology in college. He was an erudite man who could give lectures and, if you were to transcribe them, you wouldn't have to change a word or a comma. And yet, we knew that he didn't write them out, because he would walk to the lecture hall with an envelope in his hand and a pencil and he would be jotting down some words as he walked, and those were his notes. But the lectures came off mellifluously, as Hamlet said, "Trippingly off the tongue." I wrote to him, and I said, "I've been gone for over three years, and I don't know what's happening in academia and in psychology. What do you recommend?" I didn't hear from him. But I did get a letter from the Menninger Clinic, from Margaret Brenman, who said that Professor Murphy had recommended that they get in touch with me, that I might want to be part of their training program.

I had read everything I could get my hands on in psychology, while in the army, including several influential works. One was *Diagnostic Psychologic Testing*, by David Rapaport, who had come to the United States as a Hungarian refugee during the Hitler era, and who was, I think, a genius. At that time, Gardner Murphy had sponsored him, and he got a job at the Ossawatomie State Hospital in Kansas. While there, he would attend case conferences at the Menninger Clinic and became known to Karl Menninger. Menninger was another person whose works I had read. I read *The Human Mind* and *Man against Himself* while in the army. And the two, *Diagnostic Psychological Testing* and Karl Menninger's works, were as different as day and night. One was a popularizer, and the other one would brook no nonsense from anybody. I decided these were the two people I would like to learn from. So I applied to the Menninger Clinic, and after being tested by Rapaport himself with the Rorschach test, an intelligence test, and a word association test – I guess to see if my head was screwed on OK – they accepted me.

In the meantime, I was very much in love with the young woman I had been dating before I went into the army, and we decided to get married before going to Topeka. As a New Yorker, the furthest west I had been was New Jersey, until I was in the army. So, Topeka was a revelation to both of us, to my wife Ann and me. To understand what follows I need to tell you that after the war ended in Europe, General Omar Bradley was put in charge of the Veterans Administration. He was a five-star general, and he had his medical deputy go around the United States and find the best places to start hospitals, particularly psychiatric hospitals. The deputy was a man named Arthur Marshall. He was a full colonel in the European theater, but he was now back in the United

States. He stopped in Topeka to visit a cousin, who was a resident at the Menninger Clinic, and the cousin, whose name was Maimon Levitt – we used to call him Mike – arranged an interview for him with Karl Menninger. Both of these people, Arthur Marshall and Karl Menninger, were enthusiasts. And the two of them began to spin a fantasy of how it would be to have a residency training program for psychiatrists in the middle of the country, in Topeka, perhaps even in a wheat field. And when Karl Menninger said, “Well, we could take 10 residents,” Marshall said, “Well, how about 20.” The bidding continued until it was 100. And the first residency class consisted of 100 residents, MDs either fresh out of the army or fresh out of medical school, and 18 psychologists fresh out of their baccalaureate degrees, including me. And there we were, influenced by these two giants, David Rapaport and Karl Menninger.

They couldn't have been more different if one were to compare the deserts of Arabia with the tropical forests of Africa. One was a Midwestern Presbyterian who breathed good works, hope and optimism. One of his statements was, “With good psychiatric treatment, you can be ‘weller’ than well,” whatever that means. The other was a Jewish Talmudist who pored over texts trying to discern their meaning, and if you could discern one meaning, there had to be multiple meanings. These two people were my teachers. Now, Rapaport was thoroughly involved in psychoanalysis; that was the Zeitgeist then, the reigning doctrine. There was no other treatment.

TB: Are we talking about the mid-1940s?

PH: This is 1946. Deniker and Delay had not yet appeared on the international scene. We certainly didn't have phenothiazines at that time. We had no treatments for mental illness, except to talk to people. And the folks at Menninger did a good job of that. They spoke to patients. They got ideas about their lives. They even made up wonderful stories about how they became ill in the way they were. You could, retrospectively, construct that story. It was a beautiful thing. But, I grew a little restive with the idea; this is the way it is. The Freudian meta-psychology, which Rapaport was thoroughly involved in, seemed to be too much of a *fait accompli*, and the more I examined it, the more it occurred to me that this was truly a one-way street. One of my wonderful teachers, George Klein, a psychologist, first used the phrase – you could see from the meta-psychology what was happening to a person, but what was happening could not influence the meta-psychology. It was like the Torah or the Koran. It was not changeable, even though you knew that one day one might come across contradictions. At the same time, I began to see there were such things in the

psychoanalytic world as apostasies. I always thought that apostasies were reserved for the religious world, so I was uncomfortable. But Karl Menninger was an extraordinary man. He allowed experimentation to occur at the Menninger Clinic. I teamed up with George Klein, an experimental psychologist interested in psychoanalysis at that time, although he had his Ph.D. from Columbia University and studied with Salig Hecht, a very distinguished physiological psychologist.

TB: What did you team up to study?

PH: We were interested in studying perception. Not the laws of perception, but the laws of perceivers. The way, in which they see the world, in which they organize their world. We produced several experimental demonstrations that there was internal consistency in the way people see things. And we gave these consistencies names that have persisted in the literature; cognitive styles, cognitive controls, perceptual attitudes. We even used the German *Anschauung*; the way of looking at things and organizing them, the person's point of view. And we took this as far as we could, because we couldn't go further than to demonstrate there were these consistencies within a person. I was disappointed we couldn't take it further, but then I didn't realize what we needed was a new brain science. And brain science, at that time, was neurology. Neurology was almost like psychiatry, a despised stepchild of medicine. There were jokes made about neurologists. They would give you perfect diagnoses, which were totally useless.

TB: Are we now in the late 1940s?

PH: Yes.

TB: So, we are just before Moruzzi and Magoun published on the reticular activating system.

PH: Just before Moruzzi and Magoun's discovery of the ascending activating system, before recognizing that there is something in the brain that has to do with attention. Before that, attention was an amorphous concept which Freud called "cathexis." But now, Moruzzi and Magoun showed that something was happening in the brain. That was an awakening. And that was one of the things that made me realize one could take psychology just so far, and then one needed something else. But I didn't know what else. After Moruzzi and Magoun entered the scene I thought that one needed beyond psychology, neurophysiology. I also thought it could be chemistry or cell biology, I didn't know. But I knew that those disciplines were beyond me because I was a behavioral scientist at that point. I had published a number of papers on cognitive styles and a number of papers critical of psychoanalysis.

I neglected to say that I had received full psychoanalytic training and became a practicing psychoanalyst, which I enjoyed immensely, while also realizing psychoanalysis wasn't the full story. One could learn from psychoanalysis how to talk to people who were in trouble and about people who got into trouble, but I knew from my contacts with people who had serious mental disorders, like schizophrenia or major depression, that something more was necessary. Talking could help a little bit, but it couldn't do the complete job.

TB: What was your first paper?

PH: My first paper was on cognitive consistencies.

TB: When was it published?

PH: In 1948.

TB: Where was it published?

PH: It was published in the *Journal of Psychology*, and there was another one about the same time that was published in another psychological journal. My first presentation at a national meeting was also in 1948, or it might have been in 1949, at the American Psychological Association meeting.

TB: So your first papers and presentations were in the late 1940s?

PH: Yes. Within those three years, and up to the time that George Klein left Topeka, which was in 1951, I must have published about seven or eight papers. And in those days, one didn't multiply publications. I was one of the extraordinary ones because people tended not to publish. They published when they might have been startled by something a patient said. Or in psychology, they would publish a theoretical paper. But experimental papers were rare, and there were very few experimental journals. There was the *Journal of Psychology*, there was the *Journal of Abnormal and Social Psychology*, which was founded by Morton Prince, in 1909, but there were only a very few journals that published experimental literature. The *Journal of Experimental Psychology* was one of them. Today, there's a geometric progression in the number of journals, and you simply can't keep up with the literature. You read the table of contents and maybe a few papers on topics you are interested in.

TB: When did you get your B.A., in 1943?

PH: Yes.

TB: And when did you get your Ph.D.?

PH: I got my Ph.D., in 1952, from the University of Kansas. I was in Topeka working full time, seeing patients, doing research, and then at night I was traveling to Lawrence, Kansas, taking courses from wonderful people who were giants in the field at that time; people like Fritz Heider, Martin Scherer, Eric Wright, Herbert Wright, and Raymond Wheeler all very well known in Gestalt psychology. So, I got my Ph.D., then.

And as I mentioned before, I also began to write critical articles on psychoanalysis. What was my beef with psychoanalysis? It was a love-hate relationship. The beef was that it was a one-way street that you couldn't correct, and if you tried to correct it, you were called an apostate. And I thought this is no way for a science to behave. I mean, the science is psychology, the science is behavior, and every science moves by correcting and changing, even the great science of chemistry. My work became known because of the cognitive styles work.

Things began to deteriorate a little bit at the Menninger Clinic, and I began to look around. Offers for jobs had come in almost every year, but I never paid any attention to them. I would politely decline. But one came through from the University of Chicago, through Daniel X. Freedman. And he called me and told me that there was a position. Then he corrected himself. He says, "No, I'm going to create a position at the University of Chicago for a professor of psychoanalysis." I thought he was going to ask me for suggesting possible candidates, but he said, "Would you be interested in looking at it?" I said, "Well, I think you ought to know that although I am a psychoanalyst, a card-carrying one, I'm rather critical of it, and even if I still think that in the history of ideas it's a very important landmark, and one has to regard Freud as one of the major figures in psychology, I'm interested in schizophrenia now."

I forgot to mention one thing. In 1966, I got a telephone call from Charlie Shagass, who was setting up a meeting of the American Psychopathological Association, in New York, together with Joe Zubin, and they asked me to present a review paper, on perception and psychopathology. Since I had been working in perception, since 1948, and certainly knew psychopathology because I was seeing all kinds of patients every day, I accepted the invitation. And when I began to review the literature, I was appalled at what I had seen. I was impressed by something George Klein noted, in 1949. When we tried to study perception in schizophrenia, we gave it up because of the huge variances we found in patients. We didn't realize that this was a characteristic of schizophrenia. I was reacquainted with this finding in my review of the literature, and also came across several

consistent results. One was reaction time. Finger lifting reaction time was always longer in schizophrenia. The second consistent finding was that people, particularly from European countries, Poland, Czechoslovakia, and France, had reported diminished vestibular nystagmus in schizophrenia. This was also the only biological finding that Hoskins found in his study at the Worcester State Hospital, diminished vestibular nystagmus.

How interesting, I thought, a real biological finding. You can't fake that. The third consistent finding was a raised resting autonomic activation. And another one was the fact that specific responses to autonomic stimuli were diminished. So you had a raised resting level and diminished reactivity in specific responses. The last one was all of these findings, except the diminished vestibular nystagmus, could be mimicked by phencyclidine administration. So, I said to Danny, "I'm interested in schizophrenia. I've found some things that are consistent, and I'm going to present it at the APPA." He said, "Let's meet in Washington." I was on a NIMH study section at that time, and he was on another. So, we met for dinner, which was hosted by Bert Boothe.

TB: Who was Bert Boothe?

PH: Bert Boothe was a professor of English literature who was hired by Karl Menninger to become the Dean of psychiatry at the Menninger Clinic, because they had 100 residents and 18 psychologists, and needed somebody to organize the program. Bert Boothe also gave courses in English Literature, on Shakespeare and the Elizabethan poets. After a while, he started a NIMH supported career scientist program. I think Danny was on that study section, and Bert was the executive secretary who was in charge of it all. So Bert raised my name in becoming part of that program. Danny and I just hit it off; a kind of chemistry took hold. So I went to Chicago.

TB: Are we now in the mid-1960s?

PH: We are in 1968.

TB: You mentioned the consistent finding of diminished vestibular nystagmus in schizophrenics that had a great impact on your future research. When was the first paper on that published and by whom?

PH: The first paper was published, in 1921, by Pekelski and the second one, by the Detroit group, Luby, Rosenbaum and others.

TB: Did Luby's publication have an impact on you?

PH: It did have a great impact. When I got to the University of Chicago, I began to establish a way to work on vestibular nystagmus. I went to the department of otolaryngology, found a guy named Fernandez who was an expert in the vestibular system of lower primates, and told him about these studies. By that time, there were about 12 studies showing diminished vestibular nystagmus in schizophrenia. And he said, "You know, it's very interesting, but I'm so busy I can't do this. But there is a man coming from Detroit who might be interested. His name is Leonard Proctor. He's an otolaryngologist, and he's coming as an associate professor." So as soon as Proctor made his appearance, I got an appointment with him. I showed him the articles from Pekelski on vestibular nystagmus, and he was interested. He said, "Well, let's see if it's true." And he showed me how to test vestibular nystagmus by caloric irrigation.

Then I called Roy Grinker, who was the chief of psychiatry at the Michael Reese Hospital at the time and made him interested in this idea. I said, "Here are some clear findings. Let's see if it's true." Roy jumped at it. He said, "I'll send you five schizophrenics," and we examined their vestibular nystagmus response to caloric irrigation. Now, to show you that science proceeds at times by error, because you misunderstand something, here was a monumental error we made. We thought nystagmus consisted of a slow eye movement in one direction and a rapid eye movement back in a sawtooth pattern, so we looked at each of these components separately to see which was impaired. I went to the fishing supply section of Sears Roebuck, bought some fishing line and a sinker, and knowing the law of the pendulum I measured how long the pendulum should be in order to go back and forth in a cycle of about 2.5 seconds. We had the person follow the swinging sinker suspended from the fishing line. And then, we put two dots up on the board, and we would have the person look at the two dots, back and forth, as rapidly as they could. We didn't know that vestibular nystagmus is regulated mostly in the cerebellum and following a pendulum is more of a cortical function. So, what we found was that all five of the patients that Roy Grinker had sent to us had perfectly normal vestibular nystagmus, but their smooth pursuit eye movements were abnormal, as judged by the two observers. We recorded these eye movements on a polygraph.

Now, why did we get normal vestibular nystagmus? Because we thought we were controlling all the variables that could affect nystagmus. We knew, or Proctor knew, that attention and staring affect eye movements. Now, every ballet dancer and figure skater knows if you fixate as you twirl around, you diminish nystagmus, and pilots know this as well. So when people test

nystagmus, they give them little insignificant attentional tasks, like asking them “what did you have for breakfast,” or to name all the countries that start with the letter C, so they have to think of the answer. Going back to that old literature, most of the patients were catatonic and notorious for staring. Their attention is somewhere else. So, if they don’t pay attention, and they stare, they diminish nystagmus. What we did was prevent them from staring by having them keep their eyes open and putting on goggles – Frenzel lenses. When we asked them distracting questions normal nystagmus resulted. However, the smooth pursuit eye movements were abnormal. This impressed me. I couldn’t understand it. I went to Danny and said “five out of five is unusual in anything, especially in schizophrenia. I’m not sure I believe it. I think we’re lucky. But I need money.” So he went to a man named Goldblatt who owned several retail stores in Chicago, who gave me \$10,000, with which I bought a polygraph and hired a research assistant. We began to test schizophrenics for smooth pursuit eye movements and for vestibular nystagmus. And we found that smooth pursuit eye movements were disordered, not to the extent that we had first found, but quite a lot of schizophrenic patients showed it. We then used this preliminary data to get a NIMH grant. Previously, my application was turned down because they thought that my proposal was crazy and would never work, but now I had more than pilot data, so I got the grant. In our study, we found that in recently admitted schizophrenics, what people called acute schizophrenics, the abnormality was present in about 50%, and in the dilapidated schizophrenics at the Manteno State Hospital, outside of Chicago, over 80%. Can you imagine how lucky we were? We would have pursued the project even if we had found just a few with abnormal smooth pursuit eye movements.

TB: Were you relying on the hospital diagnosis of schizophrenia?

PH: The hospital diagnosis. If these people were in the hospital so long, the likelihood was that they were schizophrenic. That was before DSM-III was introduced.

TB: Are we in the late 1960s?

PH: We are in the late 1960s and 1970.

TB: Ten years before DSM-III.

PH: Another thing I got from Topeka and took with me was that when I talked with patients, I also talked with family members who came to visit. And I was impressed that some of these family members were strange indeed. Some of them, although they were not clinically ill, spoke elliptically, but then so did Danny Freedman. But Danny knew what he was doing. And many of

them misused words. Some of them were even funny looking, which today we would refer to as having craniofacial dysmorphic features. So, when I got these findings, I thought I must test the relatives for abnormal smooth pursuit eye movements. We found in recently hospitalized schizophrenics, there were about 52% with abnormal pursuit eye movements, and about 40% of first degree relatives of the patients also had abnormal movements. We couldn't get the relatives of those at the Manteno State Hospital. At this point in our research, we started to test the patients for formal thought disorder as conveyed in verbalization, in the way I learned from David Rapaport.

TB: In the processing of ideas?

PH: Yes, we looked past the content to the form of thinking. Now all of us are taught to look past language to the ideas. So we developed a systematic way of scoring formal thought disorder. Now other people have done this too, it was not unique. We don't claim that our test is the best, but ours showed that thought disorder is not a unitary thing, that there are many different kinds, ranging from peculiar use of language and words to neologisms, coining new words, to confabulations and to fusing two ideas with each other. There were 23 formal thought disorders we could identify.

TB: So you developed a method for identifying formal thought disorder and differentiating between different kinds of formal thought disorders?

PH: We developed a scoring system you could use. For example, we could take the transcript of our interview and rate it for formal thought disorder. We used the Rorschach test; the person was asked to respond to what they saw in ten amorphous forms in a standardized way, but not as a Rorschach test. And it has been quite successful. It allowed us to distinguish schizophrenic from manic thought disorder, and from the kind of thought disorder that one would see after right hemisphere damage.

TB: You supplemented the clinical diagnosis with a formal thought disorder score?

PH: Yes. And at McLean Hospital, there were physicians who would call on my associate, Dr. Deborah Levy, to give this Rorschach to differentiate schizophrenia from bipolar or other disorders.

TB: By using this test you knew the patient had a schizophrenic type of formal thought disorder?

PH: Yes. In the first paper we published in *Science*, we suggested that smooth pursuit eye movements are disordered in schizophrenia. The second paper was in Danny's journal, the

Archives of General Psychiatry. In this paper, we showed that the relatives of patients also showed the abnormality. Then, we classified patients on the basis of their thought disorder index. And the association between the abnormality and the thought disorder was even stronger than with schizophrenia, although today this would not necessarily be the case. In those days, we didn't have DSM-III. We also did a number of studies trying to disprove that the abnormality of smooth pursuit eye movement was pathognomonic of schizophrenia. We knew that brainstem lesions, hemispheric lesions, Parkinson's disease, and multiple sclerosis could also produce this abnormality. But the relatives of someone with Parkinson's or a brainstem lesion do not show the abnormality.

TB: So again, in what percentage of chronic schizophrenics did you find abnormality in smooth pursuit eye movements?

PH: In more than 80 percent. There were still a few schizophrenics who showed perfectly normal smooth pursuit eye movements, just like a 15-year old normal kid. We then had to demonstrate that the abnormality is genetically determined, by showing that randomly chosen families didn't show anything. As our dear departed member, Seymour Kety, used to say, "Silverware runs in families." So we went to Norway to team up with Einar Kringlen in a study of smooth pursuit eye movements in twins, who were discordant for schizophrenia. Now, Kringlen had published, in a 1966 monograph, that between 25 and 38% of monozygotic twins were concordant for schizophrenia, and about 11% of dizygotic twins were concordant for schizophrenia. These were the lowest concordance rates found at that time with the exception, I think, of Tienari's. Remember, Frans Kallmann found concordance rates in the 80% range. So, I felt this was a good opportunity to get the discordant twins. I convinced Kringlen to work with us, and Leonard Proctor, Deborah Levy, and I tested these twins all over Norway. We found that in spite of the discordance in clinical diagnosis, there was concordance in monozygotic (MZ) twins, as if you had an autosomal dominant trait.

We then wanted to go further. We thought; let's test the offspring of the affected and unaffected twins. As you can see, we were always trying to disprove something. We found our predictions about how many should have schizophrenia and how many should have abnormal pursuit eye movements came out the way we had predicted.

Let me go back to my early childhood, because I omitted one important fact. My mother's brother was a physician, and his name was Philip, the name that I have. He was a physician who was treating young patients, pediatric patients, at the Willard Parker Hospital in New York City. And, according to family legend, one of his young patients had a convulsion and bit him. The patient had scarlet fever. My uncle contracted scarlet fever and died. This was a cautionary tale in my life: don't become a physician, you can die. And so, I always avoided the path to medicine, even though, as I tell you about my gravitation toward physiology, it seems I should have been a physician. But you can see my interest in the individual person as well as in physiology.

Now, we've kept going further and further in our research. I won't tell you more about the other traits that we looked at. But by this time, we have called smooth pursuit eye movement dysfunctions a co-familial trait, because it tends to run in families. We, then, thought we should use this trait to tell us something about the genetic transmission of schizophrenia. So we teamed up with colleagues, Josef Parnas and Fini Schulsinger in Denmark. Fini is no longer active, so we are now working with Josef only. We identified five large families with schizophrenia, with close to 500 people, and we have tested smooth pursuit eye movement dysfunction in them. And although schizophrenia was relatively rare in these families, about 6%, smooth pursuit eye movement abnormalities are about five times more frequent. So, looking for smooth pursuit eye movement abnormalities can increase the power of looking for genetic linkage. We have formulated a model with my colleague Steven Matthyse, who is a mathematician as well as a psychologist. In this model, we have a gene that codes for a latent trait – we don't know exactly what – that expresses itself in at least two different ways, i.e., as schizophrenia and as smooth pursuit eye movement dysfunction. These are independent expressions of this latent trait, so they can occur together or separately. Then this latent trait will tell you whether or not there is a genetic component. That is the model we used in looking at the Danish pedigrees.

Independently from us, a man named Volker Arolt, in Hamburg, Germany, found linkage between eye tracking dysfunction and a locus on chromosome 6P21-23. We have independently confirmed that. So, even though there is a plethora of findings about linkage, this is not just to schizophrenia. This is to eye tracking dysfunctions that occur in a family in which there is schizophrenia. We think that this is a powerful tool for further investigation. So that's the genetics.

The physiology has captured us again. What is there in smooth pursuit eye-movements that is disordered? To make a very long story shorter than it really should be, we think that what is wrong is that the capacity to judge speed, to judge velocity, to judge almost any motion is impaired. We know that vision is modular and in the cortex there are a number of regions that have to do with different aspects of vision: contrast, slant, color, movement. Now, how fast one judges a target to be moving or the direction in which it is moving is important, and it's regulated there before it's all put together as a visual percept. We've got a number of studies I would call psychophysiological, indicating that eye movements are impaired when the person makes errors in judging speed. So, we've done psychophysical judgments of how fast something is moving. We've found that the threshold, the Weber fraction, is impaired in schizophrenics and in relatives who are judging the speed of targets. And that is highly correlated with impairment in smooth pursuit eye movements.

TB: What about the effect of drugs on the dysfunction of smooth pursuit eye movements? It is a trait, so drugs shouldn't influence it. Is this correct?

PH: Drugs do not influence smooth pursuit eye movements. They do influence the clinical condition of schizophrenia, they reduce the symptoms, but they do not cure the disease. Now we have another finding, Tom. One of the control conditions we use is to have the person judge the relative brightness of two things. We found there are no differences in the judgment of contrast between normal controls and schizophrenics or their relatives. We got the idea that maybe drugs could affect the contrast discrimination of patients from the findings of a man named Bodis-Wollner at Mount Sinai Hospital, in New York, who tested Parkinson's patients and found that contrast detection was impaired. Since contrast discrimination has to do with dopamine, probably retinal dopamine, we thought we should take a look at our patients and divide them up by the kinds of drugs that they take, i.e., typical or atypical antipsychotic drugs. And, lo and behold, we found six patients who for the last two years were on no drugs. They took themselves off all antipsychotic drugs, and were doing relatively well without. What we found with those who were on no drugs was they had the lowest contrast detection thresholds. They were highly sensitive to contrast, much more so, than normal subjects. Those who were on typical antipsychotic drugs, on Thorazine or Haldol, were up near the Parkinsonian range. Those who were on atypical drugs were normal. When you average them all, they're all normal. But here drugs make a real difference. And this

relates, you remember, Tom, to the old literature which reported high sensitivity of acute schizophrenics or even chronic schizophrenics to the environment. Things bother them. They are readily distracted. Bleuler attributed this to a poor modulation of attention. And these six patients who were on no antipsychotics at all were highly bothered by everything. I am willing to wager it has to do with dopamine regulation and doesn't have anything to do with attention.

TB: So, you are trying to identify the molecular substrate involved in the dysfunction of smooth pursuit eye movements?

PH: Yes.

TB: So, you have information on the molecular genetics but are still trying to find out more about its neurochemistry.

PH: Yes.

TB: Let me switch to something entirely different. When and how did you get involved with ACNP?

PH: That was through Danny Freedman. I had been invited to give a talk at an annual meeting, I forget what it was on, and I saw Danny holding court here, and I liked the people. I liked the activity. I liked the knowledge-exchange that was going. It was exciting. I thought, I want to be part of this. Danny said, "Not yet. You're not ready." But then I became ready, and I was so pleased to become a member and then a fellow. It has been of enormous importance to me.

TB: Did you become a member in the early 1970s?

PH: Yes.

TB: We talked about your early papers. What was your most recent publication?

PH: Well, the last one was on contrast detection. We've done some other studies on thought disorder. There is a paper that came out last summer in the *Journal of Abnormal Psychology* that has to do with working memory. I had worked with Patricia Goldman-Rakic on her paradigm, applying it to schizophrenic patients. And in this paper we report that both object working memory, i.e., memory for what things are, and spatial working memory, i.e., memory for where things are, are disordered. We used a Bayesian model to help us determine whether they were both impaired to the same extent, or one was more impaired than the other. And the answer is, we couldn't tell. So we have to do more studies.

TB: Would you like to mention a couple of people you worked closely with and /or trained?

PH: Well, my close associate, at McLean, in our lab is Deborah Levy. Martha Shenton, who I think has just become a member at the ACNP, was trained by me. So were Martin Harrow, Dara Manoach, Bob Freedman, and Sohee Park.

TB: You trained many people.

PH: If I was asked to write the list there are about 40.

TB: And there are many people working with your model everywhere in the world.

PH: Many people, but surely not all were my students.

TB: What would you like to see happen in the future in your area of research?

PH: Well, of course, schizophrenia is the cancer of mental disease. I would like to see it obliterated. I originally thought it was a simple matter, but now I realize it is not. And I have realized also that you can't do it by trying to obliterate the gene, because our latent trait hypothesis indicates that there are so many components to this disorder which are not the malignant part of it.

TB: Well, we should probably conclude with this. I would like to thank you very much for sharing all this information with us. Thank you very much.

PH: Thank you, Tom.

32. TURAN M. ITIL

TB: This will be an interview with Dr. Turan Itil³⁴ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. We are at the Annual Meeting of the College in San Juan, Puerto Rico. It is December 11, 2002. Let's start from the very beginning. Where and when were you born? Tell us something about your education.

TI: I was born in Bursa, Turkey, in 1924. Bursa is the old capital of the Ottoman Empire. My family moved to Eskisehir and then to Istanbul. I finished my high school at the Istanbul High School, and subsequently went to medical school and finished at the University of Istanbul, Medical School. And, after that, I went to military service for one year.

TB: Did you want to become a medical doctor all the time?

TI: Actually, I wanted to be an engineer, but I couldn't get into the engineering school. With my awards from the high school I was ultimately admitted to medical school. At that time, in Turkey, it was easier to get admitted to medical school than engineering. After I finished my military service, I went to Germany, where I was told that one of the most famous doctors alive was a professor at the University of Tübingen. His name was Ernst Kretschmer. Kretschmer, as you may know, wrote several books. He was one of the first biological psychiatrists of the century. I stayed at the Tübingen Clinic and finished my education in neurology and psychiatry there to become a neuropsychiatrist. When I joined the University in Tübingen, we were treating patients with phantom pain. These patients lost their arms or legs in the war and felt excruciating pain in their lost limb.

TB: Are we in the late 1940's?

TI: That is the beginning of the 1950s.

TB: When did you get to Tübingen?

TI: Just the beginning of the '50s. At that time, several of my professors told me that in a new article published by French people it was reported that promethazine, called Atosil, had a significant effect on relieving phantom pain. I was told to get the information and check out

³⁴ Turan M. Itil was born in Bursa, Turkey in 1924. He received his M.D. at the University of Istanbul in Turkey and was trained as a neuropsychiatrist in the University in Tübingen in Germany. He was interviewed in San Juan, Puerto Rico on December 11, 2002.

whether we should give it to our patients. So, I did that. According to the French publication, Atosil was effective in phantom pain, but not in all patients. So we started to give it to our patients. I found it unusual that some patients responded, whereas others did not. So I asked my professors, “How can I predict which patient will show a response and which will not?” Several of them said, “There is no way to know in advance.” Then another said, “Why don’t you read this publication from Dr. Berger? He claims that electroencephalography (EEG) would show the effects of the derivatives of opiates and barbiturates, as well as of mescaline, on the brain.”

The next day, I went to Fritz Flügel and asked whether he thought I should learn EEG in order to see the effect of promethazine/Atosil on the brain. The obvious question was whether promethazine penetrates the blood-brain barrier in every patient. The EEG might show in which patient promethazine penetrated the blood-brain barrier and had an effect on the brain. He did not believe in Dr. Berger’s findings and told me that I shouldn’t bother to learn EEG. Then, I went to my neurology professor. His name was Ishman. I asked the same question, and he said, “That’s not a bad idea. Why don’t you go and learn it?” Over the next six months I started to learn about the EEG. It was at that time that the first papers on the effectiveness of chlorpromazine in some psychotic patients were published by Deniker and Delay.

TB: Could you tell us something about Fritz Flügel?

TI: Flügel was a guest doctor like me, without pay, in Tübingen, and became chairman of one of the largest neuropsychiatry departments in Germany, at Erlangen. Professor Flügel invited Bente first, and then me, to join him in his department, and one day he said to me, “We have a machine, but nobody’s using it. Why don’t you come and start to use it?” At the time, I was working with Dr. Dieter Bente, who was one or two years older than me. He was also interested in EEG but was always busy. It was just about that time that a meeting took place in Paris on chlorpromazine which Professor Flügel attended. When he returned from Paris, he was very enthusiastic and said that he wanted to talk to the Bayer people in Germany to get chlorpromazine. And indeed, a few weeks later, we got chlorpromazine and Professor Flügel said, “Let us see whether chlorpromazine has any effect on the brain.”

TB: Was this in 1955?

TI: The meeting took place in 1954, and we started to give chlorpromazine to all kinds of patients. To our surprise, we saw some effect. The findings became my first publication on a psychotropic

drug. Our paper with Bente was published, in 1954, with the title, “The Effect of Chlorpromazine on Human Brain.”

TB: Was this the first publication on the effect of chlorpromazine on the human brain?

TI: Yes. There was an Italian publication before ours of the effect on the brains of animals; ours was the first publication on the human brain. We showed that chlorpromazine produced sleep-like effects. But the effects appeared to me more than just an effect that produces sleep. And after we published our paper, we also presented our findings at several meetings in Germany. There was no interest on the effect of the drug on the EEG; all people were interested in was that it induced sleep. To show that chlorpromazine-induced sleep was different from normal sleep, we did a study in which we recorded sleep in a group of people after sleep deprivation and in another group after chlorpromazine administration. We found a significant difference between physiological and chlorpromazine-induced sleep. And, we published these findings as well. We also found that chlorpromazine had an effect in some people, but not in others, something similar to what we saw with promethazine. We compared the effects of chlorpromazine and promethazine on the EEG, and found that even though both induced sleep, the brain sleep of patients was different with the two drugs. With chlorpromazine we saw slowwave synchronized activities, and with promethazine, we saw fast activity.

TB: So, adding one methyl group to the side chain made a difference on the effect of the drug on the EEG.

TI: Exactly. In the meantime, there were important meetings taking place. First, the one in Milan, on Psychotropic Drugs, then the founding of the CINP in Zurich, and finally, the first CINP meeting in Rome.

TB: How did the psychiatric community respond to your findings?

TI: There was no response. At the time, the German psychiatric society considered pharmacological treatment a gimmick of the drug companies. There were nineteen departmental chairmen in Germany, and only one, Professor Flügel, was involved with chemicals. They called him jokingly, the “chemical doctor,” and he was not taken seriously. The first time that he was taken seriously was when he was invited to Switzerland to meet Professor Binswanger, whose daughter had schizophrenia with hallucinations. She was treated unsuccessfully with

psychotherapy, and he wanted to see whether the drug Flügel described to him would help his daughter. It did, and Binswanger was very impressed.

TB: So, Binswanger was impressed with the effects of chlorpromazine?

TI: He was very, very impressed. And of course, he was telling the other doctors and professors, so Professor Flügel started to have a reputation. Before that, it was based on introducing occipital (cisternal) pneumoencephalography. Prior to that, pneumoencephalography was always done by lumbar puncture. He used occipital puncture because prior to becoming a neuropsychiatrist he was a neurosurgeon.

TB: So, it was Flügel who introduced cisternal puncture. Was cisternal puncture, rather than lumbar puncture, used at the clinic?

TI: Yes, it was routine in our clinic, but not in every clinic in Germany. Lumbar puncture is still used a lot, because cisternal puncture has some dangers.

TB: It's very simple to do.

TI: Yes, and much less painful for the patient.

TB: There are much less after-effects.

TI: The after-effect is little because you need to inject much less air.

TB: Am I correct that you did your EEG studies with chlorpromazine in collaboration with Bente?

TI: Yes. In 1957, there was a meeting in Milan and Flügel took me along. It was the meeting where it was decided to found a society that was to become the CINP. It took place in a small room at the university.

TB: So you are one of the few people who attended the meeting at the Milan symposium that led to the founding of the CINP?

TI: There were no more than 20 people there.

TB: Can you recall the names of the people?

TI: No, I can't.

TB: I'm sure Trabucchi, who was president of the Milan symposium, was there, and also that Garattini, who organized the symposium, was there.

TI: I remember that there was a long discussion about whether it should be a society of brain pharmacology, neuropharmacology, neuropsychiatry, or psychopharmacology. I think my boss and I were the only ones from Germany, there, but I am not sure. The majority of the people were

from Italy and Switzerland. There were also a couple of people from France and the United States. We really didn't understand what was going on. As a matter of fact, we were there accidentally. We were walking somewhere with my boss, when somebody said, "Oh, we have a meeting to form an organization." My boss shook his head and asked, "What organization?"

TB: This was in the spring of 1957.

TI: Yes. And then, we heard that in 1958, there would be a meeting in Rome. And the Rome meeting was probably one of the most important meetings in my life, because it was at that meeting that I presented on the differences in the effect of chlorpromazine and promethazine on the EEG. And just before I presented, Dr. Max Fink presented his findings. He described the effects of chlorpromazine on the brain, and that the effect of chlorpromazine is different from the effect of anticholinergic drugs. I presented my findings with chlorpromazine after him, and our findings were identical. We both got excited that the effects of chlorpromazine were different from both anticholinergic and antihistaminic drugs. We were also excited that we could almost use each other's slides to show the effects of chlorpromazine. So, we became the best of friends, and since we were the only people in the field of EEG in psychopharmacology, we began to correspond with each other to exchange information. As you know, at that time there was no email or fax. As a result of my frustration in Germany, I started to have the idea of going to the United States to do my research in a more sophisticated setting.

In 1959 or 1960, I traveled around in Germany to show my slides to professors of physiology at universities; those famous professors looked at me, and said, "You might be right, but prove it." So I started to ask people, "How can I prove it?" And they replied, "You have to quantify your findings and apply statistics, to show that the effect is not by chance, but real. That's science." We never learned science in medical school, nor after medical school, and certainly not in our training in neuropsychiatry. In Erlangen, we were working very closely with Bayer. As a Turkish citizen in a German university, you could neither get an appointment, nor be paid. So I was studying Bayer drugs at the University in Erlangen. At that time, everybody was looking for something better than chlorpromazine and for better methodology to study these drugs. We were, scientifically, absolutely like lay people. One of the scientists at Bayer, named Friedrich Hoffmeister, was a corresponding member of the American College of Neuropsychopharmacology; he was one of the top researchers at Bayer. He started to teach me

about scientific methodology. At the time, Bayer was interested in studying piperazine phenothiazines.

TB: Could you tell us about the piperazine phenothiazines you worked with?

TI: One of them was Stelazine.

TB: We are in the late 1950s. Correct?

TI: Yes. At the time we thought that more effective drugs would have greater EEG effects. One of these drugs was called butaperazine; it had a greater EEG and behavioral effect. Clinically, it turned out to be a very effective compound.

TB: Butaperazine was studied but not introduced into clinical use in North America. I am wondering why?

TI: Butaperazine came to this country but not sold because, in the meantime, Stelazine was of interest. Butaperazine produced more extrapyramidal side effects than any of the other compounds, but as I said, at the time the idea was that one would have better therapeutic effects with compounds, which induced more extrapyramidal side effects. With that kind of belief, we started to study the effects of reserpine. Reserpine was first introduced in Germany as an antidepressant, but Professor Flügel found it had therapeutic effect in psychotic patients.

TB: Reserpine was given for treating neurotic depression in some countries in those years, right?

TI: Yes, I think it was given to patients with neurotic depression.

TB: At the same time, it was also reported that it caused depression when used in the treatment of hypertensive patients.

TI: We studied the effect of reserpine in psychotic patients, especially in schizophrenics, and we thought it was more effective than chlorpromazine. We had also seen more extrapyramidal side effects with it. Professor Flügel combined reserpine with chlorpromazine and found that the combination was better than either of the two drugs alone. But it also induced more Parkinsonian effects. We presented and published our findings, but then within six months, seven patients committed suicide while taking reserpine. At first, we couldn't link reserpine with the suicidal attempts, because many of those patients were receiving other drugs as well. But by giving only reserpine to some patients, we observed that not only their suicidal thoughts increased, but also their energy level. So it was not a depressive effect alone, but together with an increase in anxiety and drive that led to suicide.

TB: Was it akathisia you saw with reserpine?

TI: Yes, patients had akathisia, anxiety and restlessness; they could not sit still.

TB: Were you the first to report it?

TI: Yes.

TB: This was in the late 1950s. How did it show up on the EEG?

TI: That was very interesting. When we did EEGs with the reserpine and chlorpromazine combination, what we saw was an increase in synchronization in the frontal area, the kind of effect seen in Parkinson's disease. In our model, that was supposed to be an indicator of better therapeutic effects. We thought the more we can change brain function, the better the therapeutic effects would be. And the changes we produced were in the direction that chlorpromazine alone had produced. It was about that time I started writing my thesis on the effect of drugs on the EEG as the prerequisite for being appointed as dozent. One area I was especially interested in was the identification of drugs with therapeutic effects using the EEG in schizophrenia. We started to call these drugs neuroleptics to differentiate them from sedative drugs. I completed and published my thesis and became a dozent at the University of Erlangen.

TB: What year was that?

TI: 1962. My thesis was published in the form of a book in Turkey and in Germany but didn't have any impact. In the meantime, Max Fink invited me to the United States. When you become a dozent in Germany, you know that in five to six years you will become professor, even if you don't do anything, so I thought I should go to the United States to learn English and how to quantify the EEG. Max was working at the time with electronic frequency analyzers.

TB: Was Max Fink in St. Louis at the time?

TI: No, Max was in New York, in the Great Neck area. It was just about the time he got the wonderful offer from George Ulett to set up a research institute in St. Louis, Missouri. I was planning to visit Max Fink at Hillside Hospital, but about three months before my visit, he told me that he was moving to St. Louis. He was planning to bring famous people, young people, from all around the world. I told him that I'm not so famous, but active and he said I should come to St. Louis.

For me, of course, New York was a very attractive place; I didn't have any idea about St. Louis. One day I was sitting at the Rotary lunch, in Nuremberg, and next to me was a young man

whose father had the biggest brewery in the city. While I was talking to him, he said he had just come from Missouri, where he visited the Busch Company, the famous brewery in St. Louis. I said, "I'm going to go to St. Louis.! What kind of a city is it?" He shook his head, "It's terrible; cold, with lots of snow in winter, and hot and humid in summer." I was shocked, but we had already planned our trip and were ready to leave.

I asked the University for a leave of absence for the year, and they approved my request. Then, a very important thing happened. Bavaria did not have any rules that foreign citizens couldn't become dozenten, so as soon you were appointed you automatically became a civil servant with pay. So, as it turned out, I became not only a dozent, but also an employee of the department and clinic. That was a big thing because I could go on sabbatical for a year. Now, sabbaticals are usually with pay, but because I was not a German citizen as yet, they didn't want to pay me. In the meantime, Max Fink offered me \$18,000 a year. I didn't know how much that was worth, so I wrote to my brother who was living in Toledo, Ohio, and asked him whether I could live on that money with my wife and my son. He wrote back saying, that's fantastic! He had been in the United States for thirteen or fourteen years and was making only \$12,000 a year. So, he told me that would be great money, and I should come immediately. So, that's how I decided to come to the United States for one year.

But when I arrived to St. Louis, I was shocked. In Erlangen, we had 150 beds and our EEG laboratories were working steadily. This was not the case at the Missouri Institute of Psychiatry. The name was great, the building was great and brand new, but there was nothing else. There were no patients and there were no machines. There was nothing. I said to Max, "What's going on?" He said, "Wait, I have lots of money. Just tell me what you need." I said to Max, an "EEG, of course." He replied, "No problem, just get the information about what kind of machine you want and we'll get it." Indeed, there was a lot of money from the state, a lot of space and plenty of patients, because the Missouri Institute of Psychiatry served nine state hospitals. Ulett was Commissioner of Mental Health for Missouri, and made Max Fink, Director of the Institute, so he could get patients from the state hospital system. Ulett was also professor at Washington University, and had Max appointed professor in the department. The plan was to create the necessary environment for research.

I was anxious; thinking I had only twelve months and that might not be enough to set up a laboratory, learn English, and how to quantify the EEG. While Max was recruiting Sam Gershon from Australia and young people from around the world, he told me I should write an application for a new grant. I had no idea what a grant was or how to write one. But of course, he helped a lot with writing it. In Germany, we had studied treatment-resistant schizophrenics and found that those with enlarged third ventricles and abnormal EEGs did not respond to butaperazine. We published our findings and Max and George Ulett read our reports.

TB: When did you publish those findings?

TI: 1958, 1959. Recently others found similar findings with MRI and CT scans.

TB: Similar to the findings you published in the late 1950s?

TI: After they read the German results, they thought it was very interesting and suggested, "You should write a grant application to study schizophrenia and psychopharmacology." After I wrote the grant, Jonathan Cole, himself, came with a group of people to review our request. It was approved for \$70,000 annually, for five years. In addition, Max had other grants. We had plenty of money. My time was up by then and I was supposed to go back to Erlangen. I had a very difficult decision to make; whether to go back to Germany or stay in the United States. I returned to Germany with my wife and told Professor Flügel I was entertaining the thought of staying for one more year in St. Louis. I'll never forget his expression; he looked at me and said, "You are crazy. You worked like a slave for many years and now that you have become a dozent and will be a professor in two or three years, you want to leave for the United States. A professor in Germany is close to God; what do you want to do in the United States? Forget it." But his wife was much more understanding. She said, "People say to do research in the United States is much better than here." My wife who was critical of everything when we arrived in the States, by the end of our year in St. Louis, started to accept the American way of life and suddenly didn't like her native country. That was crucial, and when we went back to St. Louis, we started to look for a house. Our family was growing as were the laboratories at the Institute.

We started our psychopharmacology research in schizophrenia and that turned out to be a major project. Just recently, somebody became interested in writing my biography, and when he asked me what I would consider my greatest achievement, I told him it was the quantification of the EEG. Max Fink was heavily involved with computers and we used them to analyze our data.

TN: What other important findings did you have?

TI: We discovered that all drugs that are effective on behavior have an effect on the brain and this effect can be demonstrated by using the quantified EEG. Probably even more important, were our findings that drugs which have certain therapeutic effects show similar EEG changes. All antidepressants produce one type of effect; all neuroleptics produce another type of effect; all anxiolytic drugs produce yet another type; and all drugs we call cognitive activators or psychostimulants produce a fourth type of effect. So we published our findings which showed that drugs produce different effects on the quantitative EEG if they have different therapeutic properties.

TB: When did you publish these findings?

TI: In 1965–1966. About the same time, we accidentally discovered Tacrine that was to become the first anti-Alzheimer's drug. We were working with schizophrenic patients who had cognitive deficits and were trying to figure out how to treat patients who seemed also to have – as indicated by their large ventricles and EEG changes – an organic state that interfered with the therapeutic effect of neuroleptics. We gave this kind of schizophrenic Ditrin, a potent anticholinergic substance, to make them acutely psychotic and then treat them with neuroleptics.

It didn't work, but when we gave them Tacrine, (tetrahydroacridane), a substance Sam Gershon brought from Australia; it controlled both their psychosis and confusion. It also reversed the EEG changes induced by Ditrin. We published our findings in 1965. We wrote that Tacrine had a significant effect on human behavior and reduced experimentally-induced confusion. We were not smart enough to relate experimentally-induced confusion to dementia. It was several years later that Bart Summers recognized the potential of Tacrine and pharmacologically similar drugs in the treatment of dementia. At the same time we found that schizophrenic patients have different EEG patterns from normal subjects. Then, we looked at psychotic, schizophrenic children and found similar differences between schizophrenic and normal children as we found in adults.

Finally, we took part in a WHO project in Copenhagen, with Sarnoff Mednick and Fini Shulsinger, and found that children at high risk for schizophrenia have significantly different EEG patterns than normal controls. They have more fast activity in their EEG. Since all neuroleptics decrease fast activity and increase alpha activity, they correct these EEG changes in schizophrenia. Now, twenty-five years later, we recognized a similar pattern in patients with Alzheimer's disease,

where all cognitive enhancers that exist today, including memantine, increase alpha activity that is proportionately reduced with the severity of dementia. So, as in schizophrenia, in Alzheimer's dementia, one can use EEG to measure therapeutic effects. TB: How do you predict whether a drug will be therapeutic for a patient, using the EEG? TI: Using a single test dose, you can predict whether a particular drug will produce the desired therapeutic effect in the central nervous system of a particular patient. You can see whether the drug modifies brain reactivity in the direction of normalizing the EEG. Based on this, we think that one can predict whether a particular drug will be effective in a particular patient. We call this method the test dose procedure of the quantitative pharmaco-EEG. We organized a society, the International Pharmaco-EEG Group (IPEG) and developed databases, like fingerprints, for antidepressants, antipsychotics, anxiolytics and cognitive activators.

TB: When and where did you move from St. Louis?

TI: In 1973, I moved to the New York Medical College, to Al Freedman's department because Max Fink had left the College and moved to Stony Brook University, on Long Island. I set up laboratories at the College and at the VA and we established databases for findings with drugs on the quantitative EEG.

TB: How many drugs did you study and have in your database?

TI: We studied about 250 experimental drugs.

TB: Is your database accessible to everyone?

TI: Naturally. Many of the drug profiles are published.

TB: Would it be correct to say that clinical improvement is reflected in the EEG changes?

TI: That's right, and I thought the EEG was important in the detection of the psychotropic qualities of drugs. For example, we examined hormones and found that mesterolone, a synthetic androgene preparation, in low dose, shows an anti-anxiety pattern, and in high dose, an antidepressant pattern on the EEG. The antidepressant effect of mianserin was discovered by this type of screening.

TB: We are running out of time. Is there anything important we left out you would like to add?

TI: When we published our findings, all the drug companies wanted to have their drugs studied with quantitative EEG. We couldn't do this because studies with computerized EEG are very expensive. In the 1980's, the new computers completely changed the picture, and this was the time I moved into research and set up studies with Gingko Biloba in Alzheimer's disease, and also

organized a multi-center trial with amitriptyline in a WHO program to show that its therapeutic effect can be predicted by EEG analyses. In the WHO study, we enrolled 450 patients. In the Alzheimer's study, we had 310 patients. I hope, one day, psychiatrists will be able to give a drug and be able to predict, with an automated EEG, whether a patient will respond to a psychotropic drug, without waiting several weeks.

TB: Am I correct that you are still active in your research?

TI: I'm very active. I am very much concerned that drug therapy is given without checking the effect of drugs on the brain. So we are setting up memory centers where we can check with our EEG methodology the effect on the brain of the drugs given to patients.

TB: On this note, we conclude this interview with Dr. Turan Itil. Thank you, Turan, for sharing this information with us.

TI: Thank you.

33. LESLIE L. IVERSEN

TB: This is an interview with Dr. Leslie Iversen³⁵ for the Archives of the American College of Neuropsychopharmacology. We are at the Annual Meeting of the American College of Neuropsychopharmacology, in San Juan, Puerto Rico. It is December 9, 2002. I'm Thomas Ban. Please tell us first where you were born and something about your education and early interests. Then we would be interested to learn how you got involved in neuropsychopharmacology.

LI: It's a privilege to be asked to join in this program. I was born in the West Country of England in Exeter, but my parents were Danish, so I'm a first generation immigrant. I was educated in Exeter, at a grammar school and at the age of eighteen, I got a scholarship to go to Trinity College, Cambridge, which was a great privilege. But, meanwhile, I had to do two years military service. It was not optional, and I joined the British navy, teaching ordinary seamen English and Arithmetic. I was posted to the Mediterranean, where I spent two interesting years, learning how to snorkel, dive, and sail the boats and forgetting all the science I'd ever known. Then, I went to Cambridge, in 1958, as an undergraduate to study botany, my boyhood passion. But after one term of botany, I decided to change subjects, because the teaching was very, very old fashioned, based on systematic classification of plants. They hadn't even heard about biochemistry, which I decided was much more exciting. So, I switched to a three year degree in biochemistry, which was, and still is, a very strong subject at Cambridge. The department was buzzing with excellent people and good teachers, so I had a very good education, and ended up in final year, doing nothing but biochemistry along with fourteen other students. During that time, I became convinced I wanted to do research. I had read Aldous Huxley's books, "The Doors of Perception" and "Heaven and Hell," which influenced me greatly. It was, to a biochemist, an extraordinary story, that a chemical like mescaline or LSD, a few milligrams of a pure substance, could alter the state of consciousness and the whole way one sees the world in such a profound way. It was almost miraculous and I thought, scientists should try to understand this better. So, I became determined to do a PhD in

³⁵ Leslie Lars Iversen was born in Exeter, United Kingdom, in 1937. After Exeter, he was drafted in the British Navy, and thereafter, went to Trinity College, Cambridge for his undergraduate education. He received his Ph.D. degree in neurochemistry from the University of Cambridge and did postdoctoral training with Julius Axelrod at NIH and at Harvard. Then he returned to the U.K. to Cambridge, where he rose to Director of the MRC Neurochemical Pharmacology Unit. He subsequently started and established the Merck Research Center in the UK. He was interviewed in San Juan, Puerto Rico on December 9, 2002.

brain biochemistry. The problem was, I also wanted to get married to my fellow-student Susan, and we both wanted to stay in Cambridge to do our PhD's, but I couldn't find anyone who could teach me brain biochemistry. I was getting quite desperate, until I met, by good fortune, my future supervisor Gordon Whitby. Gordon was a member of the faculty in the biochemistry department, but he'd been on leave in the States working with Julie Axelrod, where he had been involved in the very first experiments with radiolabeled norepinephrine and the discovery, with Julie Axelrod and George Hertting, of what is now called the norepinephrine transporter. Gordon Whitby returned to Cambridge just at the time I wanted a PhD supervisor. So, I became his student and was lucky to be exposed to the latest data from Julie Axelrod's lab at NIH. We were the first people in the UK to have radioactively labeled norepinephrine. It was very early days for the subject, and I was able to study the norepinephrine uptake process using the sympathetic nerves in rat heart, as the model. I made a detailed study of the kinetics of the process and the many drugs that could inhibit it, including the synthetic phenethylamines, and psychotropic drugs, including the tricyclic antidepressants and cocaine. I was getting exposed to psychopharmacology and had a great time for three years. Largely because of Gordon Whitby's contact with the Axelrod lab, I was able to meet Julie and to persuade him to take me as a post-doc. Then, I was fortunate to get the award of a Harkness Fellowship, a specialist fund, sponsoring Fellowships in both directions across the Atlantic, not only for scientists but for journalists and artists as well.

TB: Are we in the early sixties?

LI: I went to Julie Axelrod's lab right after qualifying for my PhD, which was 1964.

TB: So in 1964, you went to the States.

LI: I got to Julie's lab when Jacques Glowinski was there, and he and I worked very closely on catecholamine metabolism in the brain. I became exposed to the CNS part of the monoamine story and having access to radiolabeled tracers, we were among the first to do studies with them. I had a very busy and productive year and was exposed to Julie Axelrod with his unique creativity, which I'm still a huge admirer of. Just a few weeks ago, I went to Julie's 90th birthday celebration at the NIH, having gone ten years earlier, to his 80th birthday. I was delighted to see him still in good spirits and intellectually sharp. So my postdoc year in his lab was a great time for me. My PhD mentor in Cambridge changed from Gordon Whitby to Arnold Burgen. Gordon Whitby left Cambridge about half way through my PhD. Arnold Burgen had come back from the Montreal, Canada to be head of pharmacology in Cambridge. He took me on for the last year and a half of

my PhD and was an inspiring teacher. He was a friend and colleague of Steve Kuffler, the great neurobiologist at Harvard, and gave me an introduction there, so I was able to do a second year of post-doc in the States at Harvard in the Department of Neurobiology. The whole concept of neuroscience was still very new, and I think it was one of the first academic departments in the US that had a neuroscience program. That was, again, a period of great excitement. I worked with Ed Kravitz, the biochemist in the group but I also got to know many of the others; David Potter, Ed Furshpan and Steve Kuffler who was another remarkable genius in neuroscience. This was a privileged time for me. With Ed Kravitz I got to work on GABA. The group at Harvard had been working on GABA in the lobster, where the peripheral muscles have both an excitatory nerve, which we now know releases glutamate, and an inhibitory nerve. Inhibition which occurs inside the central nervous system in mammals occurs right down at the muscle level in crustaceans. GABA was suspected to be the transmitter for the inhibitory nerves, from a number of pieces of evidence the Harvard group had put together. My job was to make a final demonstration that, if you stimulated the inhibitory nerve, GABA was released. That might sound like a relatively simple thing to do, with a nice big muscle preparation from the lobster. We used the big crusher claw, which has a muscle that controls the finger in the inner part of the claw. The muscle, which weighed about a gram, was innervated by just one inhibitory nerve fiber, which we could expose and stimulate, while washing the muscle in sea water and measuring the released GABA. The problem was that trying to measure minute amounts of GABA in large volumes of seawater, which is a concentrated salt solution, proved technically very difficult. It took me and Ed Kravitz, together with a Japanese visitor Masanori Otsuka, two-thirds of my post-doc year to work out how to do this, and only in the last three months did we get some results. We showed that there was a calcium dependent release of GABA in response to stimulating an identified inhibitory nerve. This was the first real demonstration that GABA is released from inhibitory nerves. So, that was a fruitful period and a wonderful learning experience for me. My two years in the United States, from 1964 to 1966, were enormously influential, both in learning how great laboratories work and in making friends and contacts in the US, who have remained for the rest of my career. After that, I went back to Cambridge and rejoined the Department of Pharmacology, not as a faculty member but as a Research Fellow, sponsored initially by Trinity College, and then by the Royal Society on one of their endowed Fellowships. A few years after I got back, I was appointed Director of a

Medical Research Council Laboratory in Cambridge. We called it the “MRC Neurochemical Pharmacology Unit.”

TB: What year was that?

LI: It was 1970 when that started. The Unit was a self-contained laboratory in the Department of Pharmacology, funded directly by Government Research Council funds. Looking back, that was a dream job, because Medical Research Council funding was quite good, even if not enormously generous. It paid for staff, infrastructure, equipment, and all the running costs and we were able to attract a number of talented post-docs and students locally and from overseas. We had a number of very able young scientists from U.S.A., Canada, Australia, and Europe. So, I spent eleven or twelve years doing that enormously satisfying and very exciting job and during those years, some wonderful people came through the lab, like Ira Black, one of our post-docs and Ian Hendry, one of our Ph.D. students. Many, many people, who’ve later gone on to have their own independent and highly successful careers came through the lab. Tom Jessell was another, who is now doing very well in the field of developmental neurobiology. So, this was great.

TB: Did you continue your research with GABA?

LI: I continued to be interested in GABA, and we collaborated with Jimmy Mitchell in the Department of Pharmacology. We were able to do some GABA release studies from the mammalian cortex, using super-fusion techniques. We discovered the GABA uptake mechanism, which exists for amino acids, as it does for monoamines. We discovered a glycine reuptake mechanism, also. But, the two most notable events in that period in Cambridge were working on the mechanism of action of anti-schizophrenic drugs, and secondly, getting involved in the field of neuropeptides. The anti-schizophrenic drug story was started by work done in Paul Greengard’s lab at Yale, with his student, John Kebabian, who first described a dopamine stimulated adenylate cyclase in the pituitary. That was the first biochemical test tube model for a dopamine receptor, before ligand-binding studies came along. To me, it was very exciting, because I’d already been interested in the idea, promulgated by Sol Snyder and others, that dopamine was at the heart of the story in schizophrenia. A lot of indirect lines of evidence were pointing towards a key role for dopamine and for blockade of dopamine receptors in the action of anti-schizophrenic drugs, but the idea, until then, was based on indirect evidence. We thought, maybe we have, for the first time, the opportunity of testing this idea. Richard Miller, who was a very bright biochemistry

student, joined the lab as my PhD student, in 1974 or 1973, and started work on this mechanism, using the Kebabian-Greengard model, not in the pituitary, but in the basal ganglia of rat brain. He was able to show, very quickly, that a whole series of antischizophrenic drugs, the phenothiazines and the thioxanthenes, did indeed inhibit the dopamine stimulated cyclase system, and did so, in the rank order or potency you'd predict from their clinical potencies and known effects in animal models. We thought we had finally cracked the problem, and this was how anti-schizophrenic drugs work. Richard published a number of papers. But there was a problem; certain classes of neuroleptic agents didn't work in this model, notably the butyrophenones, such as haloperidol, which everyone knows to be a very potent neuroleptic, both in animal models, and clinically. These drugs just didn't work, except at rather high concentrations. And, that was true for the whole class of sulpiride type drugs, also. So, we knew we must have stumbled on only part of the story. A few years later, Sol Snyder's lab and Phil Seeman, in Toronto, finally nailed this down, by showing what we'd been studying was the D₁ receptor, and it was probable that the D₂ receptor, which they identified in radioligand binding studies, was more likely the target. And that's what everyone believes today. But we had a lot of fun with the D₁ research, and I developed an interest in schizophrenia research, which has been with me ever since.

TB: Didn't you get involved also in research with Substance P?

LI: While I was at Harvard, working with Ed Kravitz and Steve Kuffler, Masanori Otsuka from Japan was working on Substance P as a possible transmitter substance, and he maintained a strong interest in this after returning to Tokyo. He and I remained in contact about this. My own interest in Substance P stemmed largely from Masanori's very painstaking neurophysiological work, suggesting a role for Substance P as a sensory neurotransmitter. In the central nervous system, the work of Tomas Hökfelt and other Swedish histochemists mapping SP neuron groups was also important. Tomas was the first to publish a detailed map of Substance P pathways in peripheral nerves and in the many pathways within the brain. I got into this area, knowing we had to generate antibodies and immunoassays to measure the peptide. But you couldn't buy the peptide, at that time.

TB: Are we in the 1970's now?

LI: We are talking about early 1970's, when Susan Leeman in Boston had only just described the amino acid sequence of the peptide, for the first time. I wrote to a contact at the Merck Institute in

Raleigh, New Jersey. The head of chemistry there, at that time, was Ralph Hirschmann, who had made a batch of synthetic Substance P for Susan Leeman. He was very kind and gave me a 25 milligrams sample, which was a priceless treasure, because 25 milligrams was enough to sustain the entire program at Cambridge for many years. We were able to generate antibodies and to devise our own immunoassays and immunostaining. Claudio Cuello, a visitor from Argentina, made his own very detailed map of Substance P pathways in the CNS. Cuello later went to be head of pharmacology, at McGill, and still works in Canada. My student, Tom Jessell, was able to set up an in vitro brain slice SP release preparation, using a sensitive immunoassay. He was the first to show that if you took slices of brain stem, sensory nuclei, or spinal cord dorsal horn, the release of Substance P in the sensory areas was powerfully suppressed by opiates, such as morphine, and that effect could be blocked by naloxone. So, we discovered one of the possible sites of action for opiate analgesics in the CNS, at what we thought was one of the primary sensory relay stations, in which Substance P might be one of the pain transmitters. That was exciting, and Substance P was also the subject of a collaborative study, between my lab and my wife's laboratory in the Department of Experimental Psychology. She had developed her own psychopharmacology and behavioral psychology group. We were able to do collaborative studies in animals, using one of our monoclonal SP antibodies, showing that if you infused a monoclonal antibody into the brain to neutralize Substance P, stress-induced release of dopamine no longer occurred. We believed we'd identified a possible Substance P link, relevant to Substance P antagonists as antidepressants. In the early 1980's, along came a posse of people from US Merck Research Laboratories, led by Clem Stone, the head of CNS Pharmacology at Merck. They were looking to build a basic neuroscience lab, in England, as part of the company's global expansion. They wanted to be seen as a company doing research, not only in the USA and Canada, but in other parts of the world, in Japan and in Europe. They'd chosen England, as one of the first targets, knowing that basic neuroscience and neuropharmacology were relatively strong subjects there. They came to Cambridge and asked would I be willing to advise them on the project. Of course, I said I'd be very happy to. So, I advised them on the project, which was to build an entirely new neuroscience laboratory on a site halfway between Cambridge and London, and staff it with up to three hundred people, creating a major center for all basic and pre-clinical neuroscience for Merck worldwide. It was a multimillion dollar project. Of course, they were looking for someone to head the lab. I

said, initially, not me, “I’ve got a perfectly good and secure job here, in Cambridge, working for the government; wonderful people come to work for me, I only have to write a progress report once every three years, and I get a site visit once every six years.” In fact, the good times for the Medical Research Council were about to come to an end. Things were getting a lot tougher, in the 1980's than in the 1970's. Eventually, I saw that the Merck opportunity was just too good to miss. It was a once-in-a-career opportunity to do something much bigger than I’d done before, so I accepted the offer, and started working for Merck Research, in 1983. We started off in a temporary location and began recruiting people and that went well. In 1983 and 1984, there were a number of academic people looking for jobs, and the pharmaceutical industry was not actively looking for people. So, we were able to hire some really excellent scientists. We had, quite rapidly, a head count of over a hundred people, within the first two years, and by the time I’d finished, twelve years later, it was up to some three hundred people working on science. It was a big operation, and I learned what it was like to work for a big company, which was different from working for the Medical Research Council, in a number of ways.

TB: In what way was it different?

LI: First of all, we had a lot more money to spend and we could buy all the up to date equipment we wanted. I was fortunate to work for a company that was, and is, very science driven. Unlike many big pharma companies, which are dominated by accountants and marketing people, Merck has always been led by scientists; and during my period there, a scientist, Roy Vagelos, was appointed to be Chairman and Chief Executive, which was unheard of, but it worked very well. It was a period of expansion for neuroscience and a huge period of expansion for the pharmaceutical industry. It’s always nice to join an industry that is in a period of log growth! It was double digit growth every year, and if it fell below twenty percent, the Wall Street analysts would say something must be wrong. Of course, everybody knows, in their heart, that can’t go on forever, but in the 1980's, it was expected. During the period with Merck, I was able to set up a number of different projects in research. I learned the hard way about research and development in the pharmaceutical industry. When I joined, my mentor, Clem Stone, told me to expect that out of every ten projects you start, you’d be lucky if one of them succeeded and became a product for the company. Being an arrogant academic, I thought the rules would be different for me, but they weren’t. Out of all the projects I started during the twelve-year period I was there, only one of

them made it to the market, and that was Maxalt (rizatriptan), the antimigraine compound. Rizatriptan is one of the sons of Sumatriptan, the 5HT_{1D} agonist, which has proved to be a real breakthrough in the treatment of migraine headaches, with one of the first pharmacological mechanisms where you could treat the headache after it had started and stop it in its tracks. Sumatriptan from Glaxo was the first compound, but Sumatriptan had a number of deficiencies that we were able to improve on, notably, rather poor bioavailability, when given orally, and our compound was better absorbed orally and acted much faster. It has done quite well, particularly in the US.

I suppose one of our big challenges during my period at Merck was in the excitatory amino acid area. That was a field I'd never worked in before and we got into the area almost by accident. Merck had, before I came along, discovered a compound, which was called MK-801 (dizocilpine) that had been selected by classical pharmacology screening in an animal test for anti-seizure activity and it proved to be active orally as an anticonvulsant. Merck had put it into development for epilepsy and wanted to know how they could make it better. So my lab was assigned to find out how MK-801 worked. We tried a lot of different things. First, we set up a radioligand binding assay. Eric Wong, a talented young biochemist, did that using tritium labeled MK-801. We could then screen the entire Sigma catalog to see whether we could find anything to interact with that binding site, and we found that pentazocine and phencyclidine were moderately active competitive antagonists for MK-801 binding. That didn't tell us very much, because these were opiates of obscure mechanisms. We really didn't understand it. But then, we learned of David Lodge's neurophysiology experiments, in which he described in vivo neuropharmacology experiments where phencyclidine and pentazocine were NMDA receptor antagonists. That gave us a clue that MK-801 might be an NMDA receptor antagonist. John Kemp and Geoff Woodruff and others in our neurophysiology lab at Merck were very quickly able to show that MK-801 was indeed a potent non-competitive NMDA receptor antagonist. It was an open channel antagonist. In other words, the agonist had to be present for the antagonist to work. We were then able to show, in a number of animal studies, that this compound had a number of properties expected from glutamate antagonists, behaviorally. Notably MK-801 was a neuroprotective agent. We were keen on the idea that in stroke or other cerebral ischemia injuries, glutamate release might contribute to the damage. There were a number of animal models of ischemia, involving ligation of the middle

cerebral artery, or other insults to the brain to deprive it of blood flow and oxygen, and we worked with Jim McCulloch in Glasgow with those models. He was one of the experts in this area and he generated a number of examples where MK-801, given in vivo, was a very powerful protector against damage that would otherwise occur when these stroke models were performed. We could rescue up to two-thirds or more of the damage that would normally occur by giving MK-801, so we got quite excited about that. We wanted to get into the clinic and test this in stroke patients. But then, we hit a problem. John Olney at Washington University, St. Louis, who had been one of the pioneers of the whole idea about glutamate as an excitotoxic chemical in brain, published a paper in *Science*, reporting that in rats given a high dose of MK-801, one could see various signs of neuropathology in certain areas of the brain, notably, in the limbic areas in the cingulate cortex. What he observed was that some of the large neurons in those areas of the brain developed a pale structure with a large number of fluid filled vacuoles and looked pretty sick within a few hours after MK-801 administration. We rushed into the lab, repeated his findings, and found that the great majority of those neurons recovered to normal when the drug was no longer there. However, we had to admit there were a small number of nerve cells that apparently died in those particular areas of the brain. That became a very hot issue with the Food and Drug Administration, who called a halt to all companies working with NMDA antagonists, until this issue had been resolved. And, they set down a number of experiments they'd like to see done in primates and other animals before anything went into the clinic. Merck took a look at some other data that suggested a possibility MK-801 might prove to be a hallucinogenic molecule and decided to give up on clinical development. We were, of course, very disappointed by that; although, in retrospect, we now see all the other companies that tested NMDA antagonists in stroke failed miserably.

TB: What else did you do?

LI: We continued to be interested in the NMDA receptor and we were able to start developing cell models in which different subunits of the NMDA receptor were expressed. We began to look at some types of selective drugs to be worked with in future glutamate pharmacology. We did the same thing for the GABA_A receptors, an epic project, in retrospect, which started in the 1980's, and only twenty years later, is beginning to show some fruits for the Merck Research Labs. The GABA_A receptor has α , β , γ subunits, each of which is encoded by multiple genes. So, the number of possible permutations of GABA_A receptors is absolutely enormous, but we figured probably

most of these don't exist in brain and by making antibodies selective to the different subunits, we were able to work out that in the mammalian brain, there are not more than twenty or so of the thousands of permutations. So, we were able to set the foundations for subunit selective GABA_A pharmacology, which is continuing to this day, and Merck Research now has compounds in the development pipeline which stemmed from that research.

The other big focus for the Merck lab was neuropeptides. We had inherited, again, from previous work at Merck, a series of compounds that were pure, very selective, non-peptide drugs working at cholecystinin (CCK) receptors in the central nervous system and the gut. CCK is one of the gut-brain peptides. In the gut, CCK affects gut motility, pancreatic secretions, gall bladder secretions, and in the stomach, the closely related peptide gastrin, is a stimulator of gastric acid secretion. But, in the brain, CCK acts in multiple pathways. Its function is not yet understood, but satiety may be one of the systems involved. The particular focus we had was the curious phenomenon that CCK can cause panic in human volunteers. This was based on studies by the Danish scientist, Jens Rehfeld, and then, by Claude de Montigny and his colleagues at McGill, Kelly and Bradwejn, who had shown that if you give very small doses of CCK4 to human subjects by IV bolus injection, you get an almost immediate panic reaction, in a dose dependent manner. It is a remarkable piece of psychopharmacology. With clinical colleagues at Merck, and by working with Bradwejn and de Montigny and colleagues in Canada, we were able to show that if you gave the Merck CCK antagonist drug L-365,260, orally, one hour before giving the CCK4 injection, you could block the CCK-induced panic. That showed our drug worked in the right place and at the right time. Then, our clinical colleagues went on and did a clinical trial in patients with recurrent panic attacks. It was a six week placebo-controlled trial with forty patients and showed absolutely nothing. The drug did not work; it did not reduce the frequency of panic attacks or their intensity. It was a very clear negative finding. And, if you think about it, the logic was very weak. The logic says, "CCK causes panic, therefore, panic is due to CCK." Of course, the last part is a *non sequitur*. Management at Merck decided, quite rightly, that this whole program was not going anywhere and they cancelled the drug development. Despite the fact our lab in England had made a number of attractive looking second generation compounds, we had to give up that whole thing. But, that's the way it goes in the business of developing drugs. We had another neuropeptide in the lab, which was still going strongly at Merck after my departure. That was Substance P.

Substance P has been one of my interests since my days at Cambridge, in the 1970's. At Merck, we tried to find drugs that worked as Substance P antagonists. We had the belief they might act in the spinal cord or brain stem, and represent a novel generation of analgesics, working in the central nervous system by non-opioid mechanisms. That was the objective. We didn't know how to find a non-peptide drug working on a peptide receptor, so we tackled this in two ways. We tried rational drug development, using the peptide itself as a model, making peptide analogues by cyclizing some peptide analogues of Substance P. That chemistry program yielded some antagonist compounds, but these were not bioavailable. They didn't get into the brain, being peptides, and they were not absorbed orally, so they didn't really go anywhere from an in vivo pharmacology point of view. We also tried natural product screening to see if we could find a lead. That was how the cholecystokinin program had started at Merck, some years earlier. We tried to do the same with Substance P. We plugged our assays into a large lab in Spain doing such screenings for Merck, and we ran screening, which we thought at that time was on quite a large scale, about 50,000 tests a year for two years. Nowadays, you do that in one week. At the end, we had absolutely nothing, so we had to pull that program. By the late 1980's, we had to admit that we hadn't got anywhere at all with our Substance P program and were about to give it up. But then the first real breakthrough came in this area, the Pfizer SP antagonist was presented in a paper published, in January 1991. This was a non-peptide antagonist molecule with sub-nanomolar affinity for the NK1 receptor relevant to the action of Substance P. The whole field broke open from that discovery. We discovered, along with many other companies, that if we searched the Merck chemical library, using the Pfizer pharmacophore, we could pull out other compounds that had reasonable activity at the Substance P receptor, and could develop our own chemical series. We went into this in a very big way, with chemistry on both sides of the Atlantic, and generated multiple series of NK1-selective Substance P antagonists. We tested them in a number of animal tests, thinking naively, that once you had the Substance P antagonist, you'd be able to understand what Substance P was all about very quickly. And, of course, life isn't so simple. We found that in pain models, these compounds were not particularly good analgesics. In fact, in most acute pain tests, in which morphine works well, the Substance P antagonists didn't work at all. Only in chronic models of pain, did the SP antagonists appear to have some beneficial effects. More than twelve clinical trials have been reported by Merck and others for different types of clinical pain,

in which the SP antagonists have not been found to be effective pain relievers. Our original idea just didn't work, but by the time I left Merck, we'd developed another idea.

TB: When did you leave Merck?

LI: I left, in 1995. By that time, we had picked up on the idea that the vagus nerve, has a large proportion of SP-containing sensory fibers, and one of the functions of these fibers is in the vomiting reflex. The vagal nerves go to the nucleus tractus solitarius and then to the nearby area prostema and that's the vomiting reflex circuitry. We showed in animal models that Substance P antagonists were very potent antiemetic agents and they worked against a wider range of emetic stimuli than the classical 5HT₃ antagonist drugs, then the clinical gold standard. They also worked in the "secondary phase" of vomiting, seen in cancer chemotherapy with agents such as Cisplatin (cis-diamminedichloroplatinum) that can go on for several days, and is relatively unresponsive to 5-HT₃ compounds. The Merck development compound, 'Emend®,' a Substance P antagonist, went into clinical trial just after I left the company and was, indeed, very effective as an antiemetic against the secondary phase nausea in cancer therapy. It was subsequently approved and marketed. The other discovery made after that was what I call a 'rainy afternoon experiment' by one of our scientists. When you finish your week's work on a Friday afternoon, particularly if it's raining, and do an experiment because you have a good idea, that is what I call a "rainy afternoon experiment." Nadia Rupniak, in the behavioral lab at Merck, did something like that. She did a Substance P antagonist study, using an animal model predictive of anxiolytic-antidepressant activity. In the model, the infant pup is separated from the guinea pig mother and the pup emits distress, by vocalization that can be picked up and recorded. If the animals are treated with antidepressants, such as fluoxetine or with anxiolytics such as diazepam, this phenomenon can be prevented or reversed. Nadia showed that the Substance P antagonist she had available, did so in a very potent way. Then, she went on to show similar activity in a number of other of these compounds. Merck senior management took the bold move of going straight into the clinic for a trial in depression, doing a head to head comparison study with paroxetine, one of the SSRI antidepressants, and showed that the Substance P antagonist used in that study was as effective as paroxetine and lacked the sexual dysfunction side effect that seemed to affect a high proportion of SSRI treated patients. That compound went on to further development, and Merck management learned some of the rules about antidepressant drugs, namely, that they don't always work in

clinical trials. They were very disappointed by a second study done in 650 patients, a dose- ranging study, using fluoxetine as the positive comparator. Fluoxetine didn't work and the Merck compound didn't work, and the probable explanation is that the patients included in the study were suffering from mild depression, and the placebo effect, which is well known to be greatest in mild depression, killed the outcome. Having worked with neuropeptide pharmacology for thirty years, it was gratifying to see some practical outcome with 'Emend®' from all that.

Those are some of the highlights of my time at Merck. Some of the other things that could have happened, but didn't happen, might be worth mentioning. When I first joined, in the early 1980s, Merck had just completed a large scale clinical trial in the USA and Canada with one of the first SSRI's, zimelidine. Zimelidine was developed by Arvid Carlsson and the Astra Company in Sweden, and by that time it was already on the market as an antidepressant in Europe. The findings in the Merck clinical trials with zimelidine looked wonderful, with very good clinical data. I think it was a 4,000 patient, very large scale, Phase 3 study. I was there at the Clinical Neuroscience Group at Merck, when they were packing up all the papers that go from floor to ceiling for the FDA NDA submission. They hired a truck to take the papers to Washington. Merck could have been first in the U.S. market with an SSRI, but the compound developed serious complications. In Europe, there were some Guillian-Barre Syndrome episodes, and Astra, rightly decided to pull the compound off the market. So, it never got to the market in America. Merck had another shot at this, a few years later with another SSRI, fluvoxamine, licensed from Duphar, a Dutch company. That went into early stage clinical trials and caused nausea, vomiting in a large proportion of patients, and Merck stopped further development.

I've been enormously privileged to work in world class labs in the US and to work for a world class company, which has been a huge learning experience for me. A great deal of good science has come from the Merck lab, and I was given a great deal of autonomy in the scientific direction of an entirely new program of neuroscience projects.

TB: What did you do after you left Merck?

LI: I'll just add a couple of notes about my interests, since leaving Merck. Since leaving Merck, I have developed quite a strong interest in cannabis pharmacology. Again, as with many things in life, partly by accident, I was recruited by the UK Government's House of Lords, inquiry into the medicinal use of cannabis about five years ago and had to advise their Lordships on what questions

to ask and what witnesses to call on this issue. I had to learn quickly about the field, myself, in which I hadn't worked in before. I became very interested in the subject and the House of Lords produced a report, suggesting there may be some grounds for the medicinal use of cannabis in certain conditions, particularly, multiple sclerosis, and left it at that. The government of the day, in 1998, said we don't want to know about that, because we know we're not going to do anything on this issue. They looked at the medicinal use of cannabis as a gateway into legalizing the drug and didn't want to take this up. This was in 1998. And, it is interesting to see how the field has developed with the discovery of cannabis receptors, endogenous cannabinoids and the prospects of a whole new pharmacology evolving. The potential for developing new medicinal agents in this area is very great. Attitudes to the medicinal use of cannabinoids have changed quite markedly, just in the last two or three years. The Medical Research Council in Britain sponsored two quite large scale trials of oral cannabis extract vs. pure tetrahydrocannabinol vs. placebo in patients with multiple sclerosis, a 600 patient study, and in patients with chronic pain, which is a 200 patient study. This is, for the first time, a proper scale clinical study on whether cannabis works or not. There's also a commercial company in Britain, G. W. Pharmaceuticals, who are doing their own clinical trials of an herbal cannabis extract in MS and pain and a number of other indications. Our government has said that if adequate clinical data can be produced to the regulatory agencies, they will declare cannabis no longer to be an illegal drug for medicinal use, and they will sanction and license it.

That will be, if it happens, a large advance. On our side of the Atlantic, things are happening. Even politicians are getting the message that the way in which we're waging war on drugs is not working. We try to convey to young people that cannabis is a poisonous, deadly drug. This is something that is counter-intuitive to them, because they see their peers, and even their parents, smoking cannabis without harm. So, they just don't believe the government message.

TB: What are you working on right now?

LI: In my present job, I'm a part-time academic at King's College, London. In the merged medical school of Guy's and St. Thomas hospitals at Kings College we're building a new research center for age-related disease on the Guy's campus. Indeed, we have already built the center, courtesy of a large charity grant from Lord Wolfson and his Foundation. I'm trying to help them build that

into a world class center for Alzheimer's disease research, a topic which is very much neglected in Europe.

TB: So, that's what you have been doing these years?

LI: In addition, I have been advising small companies how to get off the ground in the biotech pharmaceutical area. I work with a small company in California, one in Germany, and one in Denmark. I have my own small company in England. I advise venture capital funding in Denmark. I do various things, which tap into my experience, over the years, as a scientist and as a pharmaceutical industry executive.

TB: You have been involved in neuropsychopharmacology for a long time. When did you attend the first meeting of the ACNP?

LI: I think, in the 1970's. I was invited to one of the catecholamine sessions, but I wasn't a member, until the mid 1980's. Since then, I've been a fairly regular attendee. I find it very beneficial to hear what's going on in the field. It's one of the best places for finding out what's going on.

TB: You mentioned that you had been working with your wife, who's a psychologist.

LI: Yes, Susan joined the Merck labs shortly after I moved there, and she headed a substantial group of behavioral pharmacology scientists for about nine years and left to take a Chair of Psychology at Oxford, which is where she is now.

TB: Didn't you write a book with her?

LI: Yes, in the 1970's. Susan wrote most of this short textbook on behavioral pharmacology, which we felt there was a need for, at the time.

TB: It was a very successful book.

LI: Yes, as textbooks go. More recently, with my cannabis interest, I've written a book, *The Science of Marijuana*, also for Oxford University Press, which I enjoyed doing. It was an attempt to bring a neutral scientific analysis of the evidence, pro and con, to a general well educated, but not a scientific readership. That book did quite well, going into paperback, and had a 2nd updated edition later.

TB: When did you publish your first paper?

LI: 1962.

TB: Wasn't it on norepinephrine uptake?

LI: Yes, the very first study we did was repeating some of the work done at NIH in Julie Axelrod's lab. It was on what happens when you inject radiolabeled norepinephrine intravenously into a mouse. When you inject a catecholamine intravenously, after a certain period of time, it will disappear. But that was not actually what was happening. When you inject the radiolabeled norepinephrine in a low dose and follow it over time, a lot of it disappears in the first few minutes, but almost half remains in the animal for many hours. What happens is that some the injected NE goes to the liver and gets metabolized rapidly by COMT and monoamine oxidase, but some gets taken up by peripheral sympathetic nerve endings and stays until it gets released and eventually disappears. And this takes hours. We were able to show that epinephrine was somewhat less vulnerable to uptake and retention, than NE.

TB: Where was it published?

LI: *British Journal of Pharmacology*.

TB: What was your most recent paper?

LI: If you count reviews, the one I'm most proud of is a large review on Cannabis. It was published in the journal, *Brain*, a distinguished neurology journal. It is unlike the book I wrote on the subject, a much more detailed academic review.

TB: What would you think is your most important contribution to the field? You moved in your research from uptake mechanisms to Alzheimer's disease.

LI: I think my contributions to schizophrenia were, at the time, quite important, but rapidly superseded by more important events. In the neuropeptide field, I'm pleased to have been one of the pioneers of the field, who kept with it for many years. Tomas Hökfelt and I now sit down together, and remember we stayed with this for thirty years, and we're finally seeing some results from it. So, that's incredible. We can't claim to be the ones that produced all the results, but we were there in a pioneering field, popularizing the idea. That was important.

TB: What would you like to see happen in the future in the field?

LI: I would like to see a better way of conducting clinical studies in Alzheimer's disease, which I think, is urgently needed. It's very gratifying to see the enormous basic research and pharmaceutical company effort in this area, not just treating the symptom, but the illness itself, understanding the molecular and genetic basis. We've made really big advances, but I think clinicians will admit they're still very poorly equipped to identify the right patients to treat at the

right time. If we find a new drug that interferes with the process of Alzheimer's disease, we need to identify patients in an early stage of their disease. By the time you get clinical symptoms, you've probably lost a significant amount of brain tissue, and there's no pharmacologist in the world, who's going to put that back. The challenge in this aspect of psychopharmacology is to find better ways of looking into the human brain, seeing how to visualize the amyloid, which is beginning to happen, having better diagnostic imaging and neuropsychological tests.

TB: Is there anything else we should have on the record?

LI: I'm delighted to see, in the field of schizophrenia, we finally, in the year 2002, are beginning to see the payoff from the human genome project. We're beginning to see the first real insights into the genetic basis of psychiatric illness. Schizophrenia may be one of the first and that's tremendously exciting. It's a whole new era of fresh targets and pharmacology.

TB: I think we should conclude this interview on that note. Thank you very much.

LI: It was my pleasure, thank you.

34. MURRAY E. JARVIK

TB: We are at the thirty-eighth Annual Meeting of the American College of Neuropsychopharmacology, in Mexico at the Acapulco Princess. It is December 14, 1999, and I will be interviewing Dr. Murray Jarvik³⁶ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Can we start from the very beginning? If you could just tell us when and where you were born, grew up, say something about your early interests, education, and we can move on from there.

MJ: I was born June 1, 1923, in New York City at the Flower Hospital on 5th Avenue, and I lived in New York until I was twenty-one. My family owned a small house in the Bronx and we lived there until the Depression. My father became ill during the depression, which was not a good time, so we lost our house because we couldn't keep up the payments. I come from a small family, just my mother, father, brother, and me, and my father became sick about 1935, had a heart attack, and died. He was fifty-one years old and I was eleven. We had no source of income and had to go on welfare, what was then called relief, and we were very poor. The house was taken over by the bank, and we spent the next couple of years moving from apartment to apartment, taking advantage of what was colorfully known as 'concession,' where they would let you live free for a couple of months, just to get tenants. This was during the depths of the depression.

TB: We are in the mid-1930s?

MJ: In 1935, when a cataclysmic event happened in my life. I got rheumatic fever and some of the worst sequellae, including aortic insufficiency, and rather severe heart disease. Somehow, I managed to keep going before the days of penicillin, when the only therapy was bed rest. So, two bad events happened very close together in my young life; my father died and I got rheumatic fever. At the same time, we also lost our house. Nevertheless, my mother did the best she could and, in 1939, things began to look up for us. That was the beginning of World War II, and the

³⁶ Murray Jarvik was born in New York, New York, in 1923. He graduated from City College of New York prior to earning a Ph.D. in Psychology at Berkley. He received his M.D. at the University of California at San Francisco. His first faculty appointment was in Albert Einstein College of Medicine in the Department of Pharmacology after postdoctoral training at the Yerkes Laboratory in Orange Park, Florida and Mount Sinai School of Medicine. He was then appointed on the faculty of the Department of Psychiatry at the UCLA School of Medicine for the remainder of his career. Jarvik died in 2008. He was interviewed in Acapulco, Mexico, on December 14, 1999.

depression was beginning to end because the United States was gearing up for the conflict. We moved to Washington Heights, where I went to George Washington High School.

One of my classmates was Henry Kissinger, although I didn't know him particularly well. After high school, my mother managed to get work and supported me and my brother. He was ten years older and working in the Physiology Department at Columbia University. This was on 168th Street in Washington Heights. He, also, was a major support for the family. The next big event that I remember was Pearl Harbor. At the time, I was in City College in New York, an excellent college, and I remember Franklin Roosevelt's December 7th speech. At the time he delivered it, I was in Physics class. I'll never forget that. They were showing us how sound could be converted into light waves. They hooked things up to the radio and we could see the sound converted to light waves, transmitted through a photoelectric cell. What was coming across was President Roosevelt giving his speech. So, that's how I heard about the beginning of the war. Because I had rheumatic heart disease, I wasn't eligible for the army and stayed in college. I was first a Chemistry major, but decided Chemistry wasn't what I was interested in. Psychology was more my interest, so I switched majors. I studied under some pretty good psychologists and got a part time teaching assistantship in the psychology department that had a big influence on my career.

TB: When did you graduate?

MJ: I graduated from City College, in 1944, and since I wanted to go out to the wonderful west coast, I wrote letters to colleges in California. Sure enough, there was an opening at UCLA; they needed a teaching assistant in Experimental Psychology. I didn't have any real training, but I did have a bachelor's degree, and they offered me the position. My salary was \$750 a year. That seemed like a fortune, so I went from New York to the west coast. I remember the long train trip, and the wonders of Los Angeles, compared to New York. In 1945, I started in the Psychology Department at UCLA as a teaching assistant to Dr. Roy Dorcas, who had recently come from Johns Hopkins with Knight Dunlap. It was such a different life, living in Los Angeles. I stayed in a student co-op and made a lot of interesting friends. One of the most interesting was a fellow teaching assistant, named Gordon Tompkins. He was three standard deviations above the rest of the class in his abilities and very smart. So, we got to be friends; Gordon was eighteen and I was twenty-one. He was an only child; his father was a doctor and his mother a pianist. Gordon went

on to become an eminent molecular biologist. He went to Berkeley, and I followed after I got a teaching assistantship there.

TB: When did this happen?

MJ: This was in 1945 or 1946. There was a lot of intellectual activity at Berkeley but not the radical student activity that occurred years later.

I forgot to mention one other thing. When I was living at the student co-op in Los Angeles, I met Leonard Lindey, a roommate who became another friend. There were three of us in one room, and we paid \$27 a month for room and board. I think the co-op still exists; it was a good deal!

TB: So, you made another friend, Leonard Lindey?

MJ: Leonard was an undergraduate at UCLA; by coincidence, we met again years later. I'll come back to that.

TB: So, you moved from UCLA to Berkeley.

MJ: I was a graduate student now, in Psychology, interested in Learning and Memory. I worked under Edward C. Tolman and learned how to run rats in mazes. Everybody in the department had to learn this, even if they were studying to become clinical psychologists. I was interested in Philosophy, and I'd read a lot of Burke and Russell. There was a philosopher at Berkeley whose course I took. Now, I'm 76 years old and I can't remember his name; although he was well known. He was teaching probabilistic positivism and that interested me a lot. So, my Ph.D. thesis was on gambling, gambling in rats, mind you, and also in humans. My first paper was on "*The Gambler's Fallacy*." It was based on the thought that if you toss a coin and it comes up heads three times in a row, you're going to bet it's going to come up tails the next time. That's a fallacy, of course. I did work under another psychologist, named Agon Brunswick, who became my thesis chairman. Brunswick had come to this country from Vienna. He was actually a Baron. Agon Brunswick was a fascinating teacher with a strong philosophical bent, interested in Probability Learning. I became interested in Probability Learning and, by coincidence, went to work as a research assistant for his wife, Elsa Frankel Brunswick. At the time, there was a big project on Racial Prejudice.

TB: When was this?

MJ: This was in 1946 or 1947. This wasn't long after the Nazi era ended in Europe, and there were a lot of very intelligent refugees from Germany and other parts of Nazi occupied Europe at

the university. Elsa Brunswick was Jewish, Agon Brunswick wasn't, but he left Germany because of her. It was my good fortune to work for both of them. Then, something else happened in my life, which was unexpected. It shows you how bad things can sometimes turn out to have good fallout. I came in contact with a social worker. I told her I had rheumatic heart disease, and she said, "Well, you may be eligible for some kind of support for vocational rehabilitation. We can send you to school. What kind of school would you like to go to?" I said, I'd like to go to medical school. Sure enough, in those years, the rules were such that she could get support for me in medical school, at least for tuition. I had not even dreamed I would be able to afford to go to medical school, so this was a wonderful thing.

TB: What year was that?

MJ: This was in 1947. In the meanwhile, I had worked towards my Ph.D., but hadn't finished. Still, I took advantage of the possibility to go to medical school.

TB: So, you went to medical school. Where?

MJ: University of California, San Francisco. At that time, the first year for both schools, was at Berkeley, so I stayed there. The first day I registered I met Leonard Lindey, who, as I told you before, was one of my roommates at UCLA. We decided to be partners in Anatomy, worked on the same cadaver, and became very good friends over the next four years. During this time, I spent the summers back in the Psychology Department, where I could work on my thesis and do a little research. It was pretty clear to me I was going to specialize in some kind of research, probably related to behavior, even though I was also going to get my M.D.

TB: When did you get your M.D.?

MJ: I got my M.D., in 1951. Leonard and I kept in touch, off and on all these years, and just recently he told me that next year we've got to celebrate our fiftieth anniversary, "It's going to be our fiftieth, 1951 to 2001, the year after next." I said, "Yes, if I'm still alive," and there was some question about that.

TB: What did you do after you finished medical school?

MJ: When I finished medical school, I felt I'd like to find out what goes on in the brain; when and how something becomes a memory. The reason for that was I'd been running rats with Dr. Tolman and the other people in the psychology department and all of them were interested in learning and memory. There was controversy at that time about the nature of learning in memory, with Tolman

having one theory and Clark Hall at Yale having another, and of course, those of us at Berkeley were very biased toward the Tolmanian theory. But all those theories were superficial. This was black box psychology; people didn't know what was going on in the brain. I thought, there must be somebody in the country that is looking into the brain, and of course, there was. He was Karl Lashley, professor at Harvard, at that time. So I wrote to him and asked if I might have a job with him. And, as luck would have it, he did have a job for a research assistant in Orange Park, Florida at the Yerkes Laboratories, which was a monkey and ape colony. Lashley had a grant from the Navy to do brain operations and see how this would influence learning. He had already established a name for himself doing brain operations in rats and just about the time I met him, he came up with a theory of equipotentiality, which I think has been largely disproven over the years, but at that time, it was considered to be good stuff. So, I moved from Berkeley to Orange Park, Florida.

TB: What year did you move from Berkeley to Orange Park?

MJ: This was in 1951 or 1952. At that time, Orange Park, which is a suburb of Jacksonville, was part of the deep-south. There was no institution of higher education in Jacksonville, except the Jacksonville College of Music, which was a small place where Lashley used to go to practice his cello. The Yerkes Laboratory was also out in the country. There must have been a hundred chimpanzees and a large colony of monkeys, so, I started to do some brain surgery on monkeys with Lashley. But after a short time, I decided I didn't like the sight of blood. It was amazing how Lashley operated. He didn't use any sterile technique and there was no air conditioning in those days. I remember to this day the sweat pouring from his brow into the wound, while he he was operating on a monkey's brain, but the monkeys always seemed to survive anyway. At that time, I got interested in One-Trial Learning. There was a lot of interest in Wisconsin in learning because of Harry Harlow. It took hundreds of trials to train monkeys to do a simple discrimination, but I found if I used colored breads, flavored with capsicum or quinine, they could learn in one trial. Unfortunately, another bad thing happened to me while I was at the Yerkes Laboratory.

TB: What happened?

MJ: There was some land for sale near there. I bought ten acres of land for \$27, and thought I'd put a trailer up and live there, rent free. I did that, but one day I found I was unable to get out of bed. I couldn't move, had a high fever and was alone. I was just lying there and thought, I'm going to die. I can't move. But, after several hours, one of my colleagues noticed that I didn't

come to run my monkeys. I ran my monkeys seven days a week and when she noticed I hadn't showed up, she and her husband came out to my trailer and found me. They took me to the hospital.

TB: What did you have?

MJ: I had bulbar polio, and this was before the Salk vaccine. I managed to miss two important things, penicillin for rheumatic fever and the Salk vaccine for polio. In a way, I was lucky, because the polio didn't kill me. It was only bulbar. The rest of my body was OK, but my vocal cords and my swallowing apparatus were partially paralyzed and I couldn't talk for a while. I recovered, mostly, but I've never recovered fully. I still have trouble talking and I'm only speaking with one vocal cord. Things were so bad that my brother, who was living in Stanford, said you've got to come to Stanford and recuperate here. So I did. I had been at Yerkes for about a year and a half and it was time to leave. I looked for a new position and found one in New York. Heinz Lucas Tarboro was a physiological psychologist, very much interested in the brain, and he said, "Well, there's a position opening at Mt. Sinai Hospital and maybe we can get you a job there." It was an interesting job, indeed. I went to see Dr. Hoffman, who was the head of psychiatry at that time at Sinai, and he said, "You can become a Fellow in the psychiatry department and work here at Mt. Sinai Hospital; we have a special project we would like to put you on."

TB: What was the project?

MJ: It was the study of a new drug, which they'd just heard about. This was in 1952. The substance was called LSD-25 (lysergic acid). They told me a little bit about it as well as about Hoffman's work, and I thought, that sounds fascinating, I'd like to work on that. The fellow in charge of the project was named Harold Abramson. He was the one who actually hired me and paid my salary, even though I was stationed at Mt. Sinai Hospital. Harold Abramson was an unusual person. He was a physician, who was really a physical chemist, but also practiced psychoanalysis. I didn't know then how he was able to get money for his research from a wealthy donor, whose name, he told me, was Dr. Geschichter "Is that really his name?" I asked; and he said, "It is, and we're going to have a meeting with him." Sure enough, Dr. Geschichter from Washington, DC showed up and he said, "Yes, we are going to study this new drug. It has very interesting characteristics and I'm donating this large sum of money, out of which we'll pay your salary. I think it was \$6,000.00 a year, which seemed like a lot of money at the time. So, we set

up this project. I remember we were given a suite of rooms in the basement at Mt. Sinai Hospital and we advertised in the Village Voice to get subjects who were willing to take LSD.

There were no committees for the protection of “human rights,” so we got a lot of people who volunteered, not knowing what they were going to get. I must have had about a hundred subjects on 50, 100, or 150 micrograms of LSD. I remember taking fifty micrograms myself, but I didn’t get much of an effect. Some of our subjects did get hallucinations and disturbances of thought and my job was to to examine the changes in psychological functioning the drug produced. I worked with a staff and we produced a lot of papers.

TB: What kind of tests did you use?

MJ: We used a battery of tests which included reaction time.

TB: So you used a battery of performance tests.

MJ: Performance tests, primarily, and we got a dose-response relationship that was pretty good. LSD really did impair performance. Looking back, what was surprising to us was the small dose, the extreme potency of this substance. By the way, we had no trouble getting LSD. Sandoz was very cooperative. Louie Burcher, a Sandoz representative, used to come with a large valise full of LSD. We didn’t have to go through any red tape in those days, which was both good and bad.

TB: What years were you at Mt. Sinai?

MJ: I spent from 1952 to 1955 at Mt. Sinai. The most interesting thing of all happened in 1954.

TB: What happened?

MJ: I met my wife, Lissy Jarvik, who was an intern at Mt. Sinai Hospital. She had wandered into my lab, lost somehow, and we got acquainted. One thing led to another; it was a very lucky thing for me. We were married at the end of 1954. That was just about the time I was ready to leave Mt. Sinai. I got a lead from somebody that there was a new medical school, opening in the Bronx, Albert Einstein College of Medicine. So, I got in touch with the prospective chairman of Pharmacology, Alfred Gilman. He interviewed me and said, “You’ve had experience working on drugs and behavior. It looks like there’s a renewed interest in that. Maybe you’d like to join my new department. I replied, “I certainly would.” Gilman was already well known for his book, Goodman, and Gilman, on Pharmacology. So I went to this new school, Albert Einstein, which was part of Yeshiva University, and I was the first one, besides Gilman, in that department. Then he recruited a lot of other people, all of them very good. Gilman was very helpful to me. He told

me he was on a council at NIH and suggested I should apply for a grant. He also told me he would help to prepare it. He did and I got the grant. It was just amazing, my first grant. It was \$15,000 a year and out of that, I was able to hire two assistants to set up a monkey laboratory. \$15,000 was like \$150,000 today. That was the beginning of my career in Psychopharmacology.

He also did something else, which was very good for me. He said, “There are new drugs coming out for the treatment of schizophrenia. Why don’t you look into it, and in the next edition of Goodman and Gilman maybe you’d write a chapter on Drugs and Psychiatry”? And I did; I wrote the chapter on Psychopharmacology for the next three editions of Goodman and Gilman, which came out every five years. This was the 1960 edition, and I was able to recount the amazing advances in Psychopharmacology from 1950 to 1960, a period in which all the new drugs came on the scene, starting with reserpine and chlorpromazine then followed by antidepressants. In 1972, I left Albert Einstein after seventeen years, from 1955 to 1972.

TB: So while you were at Einstein your primary area of research was on the effect of drugs on performance tests?

MJ: That’s true. I also did some interesting memory experiments. Remember my friend, Gordon Tompkins? He was by then Chief of the Molecular Biology branch at NIH, and he said, “You’re interested in memory. Why don’t we look at the role that DNA and RNA might play in it? I’m going to put you in touch with a young psychiatrist, working in my laboratory. His name is Samuel Barondes.” Sam did experiments with some new compound, like puromycin and actinomycin. In the meanwhile, I had devised a one-trial learning test for mice. So we gave intracerebral injections of puromycin and actinomycin. Puromycin is a protein synthesis inhibitor and actinomycin is an RNA synthesis inhibitor. We found both of these substances impaired memory. We gave the injections post-trial, at different intervals, and got retrograde amnesia, which was related to the inhibition of synthesis of both protein and RNA. I was also interested in the effect of electroshock (ECT) on mice. We got a nice curve of retrograde amnesia using ECT, which bore out what had been reported in the clinical literature following ECT. This was my first paper that was published in *Science*.

TB: When was it?

MJ: It must have been around 1962 or 1963. During these years, I had a number of foreign fellows who worked in my laboratory. The fellow who worked on retrograde amnesia from

electroconvulsive shock was Rudy Kopp, from Germany, and he was senior author on the paper in *Science*.

TB: What happened to your research with LSD?

MJ: After 1970, I didn't work much with LSD anymore. By this time, LSD was becoming something you didn't work with. It had become an underground drug; Sandoz had already pulled it off the market. They weren't even making it, let alone distributing it. It had to be manufactured illicitly. So, I decided it was time I didn't work with LSD anymore; although I was interested in it and still am. It's a fascinating drug, and we don't know exactly what its mechanism of action is yet, or why it is so potent. But working with LSD played a role in my subsequent career.

TB: What was your subsequent career?

JW: Around 1970 or so, I met a fellow, who also had worked with LSD. His name was Louie J. West, Jolly West, and he was starting a department at UCLA. He was moving there, in 1969, and would I be interested in coming? I was very interested, because I was tired of New York, and the New York winters. We didn't move permanently in 1970. It was just a sabbatical year I took first. We had to negotiate for a job for Lissy, because Jolly had only offered me a job. At the end of the year, I went back to Albert Einstein and had to tell Gilman I was thinking of leaving. Then, after another year, we left for good and went to Los Angeles, where we've been ever since. Jolly managed to get a job at the VA for Lissy. We thought that wasn't so great, but it turned out to be an excellent opportunity for her. At that time, the West Los Angeles VA was affiliated with UCLA; it was the premier VA hospital in the United States. Jolly had engineered a split between two branches of VA hospitals; Wadsworth was to become the medical branch, and Brentwood the psychiatric branch. He put one of the members of his own department, Phillip May, in charge of the hospital which was great, because both Lissy and I were then able to work for Phil. But they didn't have any space for us. West said that they were renovating some buildings. There was an earthquake in Los Angeles, in 1971, and one of the buildings had been shaken up so this was the reason for renovating. Anyhow, Jolly said, "We're going to renovate this building and when it's finished, you'll have lab space in it. In the meanwhile, we'll put up some temporary trailers and you can work there." So, they built six trailers and Lissy and I each had two. The others were given to somebody else. This was 1972, and we're still in the trailers. We never moved out although there was a lot of space. Now the trailers are so old they're beginning to fall apart, but

we've had a lot of good use out of them. I just remembered another major change in my career that happened around 1970.

TB: What happened?

MJ: I got an invitation from the American Cancer Society. The background to the invitation was that a few years before, Luther Terry, the surgeon general, had issued his first report on the ill effects of smoking. The American Cancer Society knew I had been working on the behavioral effects of drugs, so they asked me whether I would be interested in working on the behavioral effects of nicotine and cigarette smoking. I thought, that sounds like an interesting idea. So, they said, "If you apply for a grant, we'll help you to put it together and see if you get it." Not surprisingly, I got the grant, and what I was planning to do was to study cigarette smoking in animals, where you can control things.

TB: What animals did you use?

MJ: What animal was the best for this? Monkeys, I thought. So at Albert Einstein, I set up a monkey laboratory with a cigarette smoking apparatus, but it turned out to be a much tougher problem than I thought. People may take to cigarettes very readily, but monkeys don't, nor does any other animal. Still, I managed to force monkeys to inhale smoke in order to get water but they didn't smoke the way humans do. Other people in the world have tried to do the same thing, but so far as I know to date, nobody has got any animal to smoke the way humans smoke cigarettes. There's one exception, and that was the thing that really forced me to continue with this monkey business; when I was at Yerkes Laboratories, there was a female chimpanzee, named Alpha, who used to smoke cigarettes. The keepers, every morning when they went around to feed them, would give her a cigarette and she smoked it just like a human being, held it in her hand and puffed deeply and exhaled the smoke. I thought if chimpanzees can do this, monkeys could do it too, but my monkeys never did. I decided there's another primate species that maybe easier to work with, and so, I switched to humans. At that time there were plenty of human smokers around. Everybody I knew was smoking. When I was in medical school, sixty percent of my classmates smoked, but I never did. When I was still at Albert Einstein, there was a visit from a Nobel Prize winner to Murdoch Ritchie's laboratory. I've forgotten his name, but he was from Sweden. Both he and his father were Nobel Laureates. When I told him I was interested in cigarette smoking, and I had smoking monkeys, he said, "Do you know we're interested in smoking in Sweden, as well, and

there's a new gum they're trying out which delivers nicotine?" And, I said, "I'm very interested in that. Could you give me the name of the person who is working on it?" And, he looked it up and gave me the name.

TB: So, this happened when you were still at Albert Einstein?

MJ: Yes. Then when I went to UCLA, I got in touch with Leo Pharmaceuticals. They were making nicotine gum and when I got to meet Dr. Ferno, the inventor of the nicotine gum, I said, "I'd really like to work with this stuff. Could I have some?" And, he said, "We'll have to set something up for you." Actually, it took a couple of years to set it up with the company that was the liaison in the United States to Leo in Sweden. They were able to supply me with samples of nicotine gum. They also gave me a little money to run a clinical trial to see if nicotine gum would be of any help in smoking cessation. I hired a very bright UCLA graduate student, named Nina Schneider, and had her to work on our clinical trials in this area. She did a wonderful job and over the next few years, I guess it must have been around 1974 or 1975, we ran a number of clinical trials for this drug company, the name of which I've forgotten. But the company, before the trials were finished, decided this was not a viable product and gave it up. It was a bad mistake on their part and maybe that's why I can't remember their name. But, Leo in Sweden, of course, never gave it up. They found a new company, Dow Chemicals, and we did some further trials supported by them. We also published our results in which we showed that the gum was certainly better than a placebo in helping people to stop smoking. So, I became very interested in nicotine, and that's been a central theme of my work since the beginning of the 1980s. One of the things I was interested in was the way of administering nicotine and I looked into this. I learned there was something called green tobacco sickness, which is a sickness people who pick tobacco get if they handle it with their bare hands. What this told me was that nicotine must be getting through the skin. So, I tried to look into a way of administering nicotine via the skin. I had another post-doctoral fellow working with me, named Jed Rose, and we figured out a skin patch would be a good idea, a nicotine patch. I told Jed if this really works, it might have some commercial value and should be patented. So, we went to the patent office of the University in Berkeley, and when we told them what we have, they said they were interested. Well, it took a long time to get it patented. We started, in 1980, and finally got the patent approved in 1990. It took ten years of incredible litigation, going back and forth with administrators in the university. We assigned the patent to the university but managed to get

a pretty good royalty from it. The university had assigned our patent to Ciba-Geigy, which was a big drug firm, and they marketed our skin patch as Habitrol. Then, Ciba-Geigy and Sandoz amalgamated and formed a new company.

TB: Novartis.

MJ: Novartis, exactly. And Novartis decided they weren't going to put it on the market. I never found out exactly why, so that was a big crimp in the royalties. But, it's still being prescribed by prescription. My research interests since the 1980s have been primarily in nicotine; how nicotine works, and the tobacco withdrawal syndrome, which is really a nicotine withdrawal syndrome.

TB: How does nicotine work?

MJ: I don't think people know yet, exactly how nicotine works, but there's a lot of evidence that one of the primary mechanisms is that it releases dopamine from its stores, wherever they are. It releases catecholamines, generally, including epinephrine and norepinephrine, but dopamine seems to be the key neurotransmitter released by nicotine. In some of our recent research, we tried to hone in on this by giving drugs, which either are agonists or antagonists to dopamine. So in recent years, we've worked with bromocriptine, which is a dopamine agonist, a drug that behaves like dopamine and we have given bromocriptine to smokers to see how it influences their habit. We have also worked with haloperidol, which is a dopamine blocking drug, to see how that influences smoking. And I've been interested in smoking in schizophrenics. They are smoking a lot; the prevalence of smoking is very high in schizophrenics.

TB: So, you studied the effect of bromocriptine and haloperidol on smoking.

MJ: We did dose-response curves with haloperidol, and we found what we expected turned out to be true; haloperidol increased the amount of smoking that people did, as though they were trying to overcome the block of dopamine receptors. We also found that with bromocriptine people smoked less. We've just published a couple of papers on the subject. Our findings support the idea that dopamine is an important intermediary in the action of nicotine. That's not all that nicotine does. It has a complicated cascade of effects.

TB: Did you continue to work in both animals and humans?

MJ: No, only in humans. In fact, I've given up animal work. I gave it up around 1980, or so. It was increasingly difficult for me to work with monkeys. It became very expensive. There were problems with possible diseases and with viruses like Ebola. So, I decided that humans were better

to work with. We had a lot of smoking humans at that time, in Los Angeles; they're fewer now, but there are still enough people.

And, I might mention one other irony in my life. Since I've been working with smoking, I work with the American Cancer Society. I never smoked a cigarette, but in 1992, I was diagnosed with lung cancer; I had a lung cancer as a non-smoker. It was successfully removed. It was localized, just one small cancer with no metastases and I was followed very thoroughly for the next five years. There was no recurrence, and I'm still around. It's almost 2000 now, and my surgeon assures me that I'm cured, and I'll accept that. But, it was an irony that I should get lung cancer; whereas, my smoking subjects didn't. I've had other health problems. My rheumatic heart disease, of course, has remained with me all my life; at one point, when I was eighteen years old, I looked up the life expectancy for people with my type of rheumatic heart disease. There was a book by Mae Wilson; and on the basis of signs and symptoms, the estimated life expectancy for people like me was only thirty-three years. I'm seventy-six years old now, so I guess it didn't work out the way it was supposed to.

TB: Let us try to recapitulate some of your research. You introduced one-trial learning and studied the effects of drugs like puromycin and actomycin on learning and memory?

MJ: Yes.

TB: You are one of the few people still around who worked with Lashley?

MJ: That's true. Lashley was already towards the end of his career when I worked with him. He was an interesting and colorful figure.

TB: Then you did research with LSD?

MJ: That's right.

TB: You also did research with the new psychotropic drugs, while at Albert Einstein, and you were the first to write a chapter on them, in 1960, in Goodman and Gilman.

MJ: Right.

TB: You covered chlorpromazine, reserpine, meprobamate, imipramine, and iproniazid in that chapter.

MJ: That's right.

TB: The benzodiazepines were just introduced.

MJ: Meprobamate was the big one, at that time.

TB: Frank Berger's drug.

MJ: You know, somebody told me Frank Berger is still alive.

TB: He is very much alive. I talked to him a couple of days ago.

MJ: Is he here?

TB: No, he's not here.

MJ: I visited with him around 1960, or so. At the time, he was the richest pharm around.

TB: I'm sure he would be happy to hear from you.

MJ: I'll look him up.

TB: Could you elaborate on some of the drugs you worked with at Einstein?

MJ: One of them was chlorpromazine, the drug introduced by Lehmann and...

TB: Hanrahan.

MJ: Lehmann used it first in North America, if I recall. That was around 1955, or one year before.

I remember going to an early CINP conference, in Rome, in the late 1950s. All of the people involved in the development of these new drugs were there. I remember Madame Curvoisier.

TB: Madame Curvoisier, the pharmacologist who worked with chlorpromazine.

MJ: And there must have been people there who worked with reserpine.

TB: Nate Kline was there.

MJ: I think, Bein from Ciba was also there.

TB: You mentioned you worked with chlorpromazine at Einstein. What did you find?

MJ: It's such a long time ago, but I remember one thing about chlorpromazine was that it was different from the barbiturates. Actually, a friend of mine, who had been working with me, named Conan Kornetsky, developed a continuous performance test, which he and I used to differentiate barbiturates from chlorpromazine; barbiturates produced a marked impairment of equilibrium and coordination, whereas chlorpromazine didn't. I did some other work, too, in which I found differences. I worked with a neurosurgeon at Albert Einstein, named Allen Rothboyd, who developed a method for injecting drugs into the carotid artery of cats and we tried to compare chlorpromazine with barbiturates. When we injected a barbiturate into the carotid artery, we got an immediate hemiparesis, a stroke so to speak, but when we injected chlorpromazine nothing happened for about half an hour, and then, slowly, the animal would start moving toward the side

of the injection. Unfortunately, Allen Rothboyd died about ten years after that, but we did publish a paper.

TB: So you also collaborated with Conan Kornetsky on the continuous performance test. Did you work with him in normal subjects and also in schizophrenic patients?

MJ: I didn't do that with him. By that time, Conan was working at NIH.

TB: Then, he moved to Boston.

MJ: Right. We've kept in touch. In fact, he organized a sort of old timer's symposium about six months ago, and I took part in it in Boston.

TB: You have been in research for 50 years.

MJ: More than fifty.

MJ: Nearly sixty years.

TB: And during those years you published many papers, right?

MJ: I have about three hundred papers.

TB: Three hundred papers. You mentioned the first that was published in Science. Would you like to mention any of the others?

MJ: The paper describing the usefulness and effects of the nicotine patch, which we published around 1984, was an important one, because it helped us get a patent. It's hard for me to pick what stands out; I have three hundred titles running through my mind. I don't think any of them are worth a Nobel Prize. The One-Trial Learning procedure, which I worked out for mice, I consider important, because up until that time, nobody had used a one-trial procedure. They'd only used multiple maze learning procedures. The fact you could have one-trial, with a lasting effect, meant you could follow it at different time intervals with treatments and get a precise measure of the temporal events following the learning trial. I think that was the most important thing that I did.

TB: Any other papers you would like to mention?

MJ: Being an early investigator of LSD was interesting, because it's a substance which had some wide sociological influences, to put it mildly.

TB: You mentioned you had no problem in getting LSD from Sandoz, and when they stopped, people could get psilocybin.

MJ: Yes, and I did work with psilocybin, and also, with other hallucinogens such as mescaline.

TB: Did you find any difference between the effects of LSD and mescaline?

MJ: I don't know that I went into it in enough depth. I did some animal studies with various hallucinogens and there might have been some subtle differences. The major effect in animal studies was impairment of performance. With humans, of course, I always used just retrospective reports.

TB: You had many people working in your lab.

MJ: That's true.

TB: So, you trained quite a number of people.

MJ: That's correct.

TB: Would you like to mention some of them?

MJ: I hate to leave anybody out, but in 1998, last year, a couple of my students or fellows decided to have what they called a Festschrift for me. It really wasn't a Festschrift. It was a party at the Society for Research on Nicotine and Tobacco, which met in New Orleans, in March. They tried to gather together all of my students or fellows, but I was very sick and couldn't go to the meeting. They arranged to make a videotape and they showed it there. This was organized by Alan Grids, who is a professor at the University of Texas, and Ian Stolerman, who is at the Maudsley Hospital, and both of them worked with me. They also got about ten of my former students and colleagues together, who gave brief talks, which were very nice. I was very sick, and it looked like I might be dying, but I didn't. I fooled them; I'm still around! I hate to mention anyone, because I'm going to leave out somebody I should mention.

TB: We talked about your papers. Did you write or edit any books?

MJ: I edited one book on Psychopharmacology.

TB: Would you like to elaborate?

MJ: That was around 1975. It was called *Psychopharmacology in the Practice of Medicine*, I think, and I had contributors like Wikler and Jerry Jaffe. About a dozen people wrote some very interesting chapters. But the book is out of print by now, as it should be, because time and science marches on, although some of the chapters by people like Wikler, are useful from a historical point of view.

TB: When did you become involved with ACNP?

MJ: In 1961.

TB: Are you one of the founders?

MJ: That's right, and the same is true of the CINP.

TB: I think you mentioned you participated in the first CINP congress?

MJ: It was in Rome, in 1958. I remember that we went to see this very controversial Pope.

TB: He actually gave a very enlightened speech.

MJ: Yes, I remember that. Now, he's controversial because he didn't oppose the Nazis like he should have, but there're pros and cons on that.

TB: Any other organization you are involved with?

MJ: The biggest organization I belong to is the American Psychological Association, because I got a Ph.D. in Psychology. So, I've belonged to the American Psychological Association for all these years. Now, I'm emeritus, I don't pay dues for many of these organizations, which is very nice.

TB: Is there anything we did not cover and you would like to add?

MJ: Just my personal life; I've been very lucky. I've been married to this wonderful woman, Lissy Jarvik, who has been with me through thick and thin. She's also a good scientist, and she became a distinguished physician in the VA. And she, of course, became professor of Psychiatry at UCLA. She's with me here, and we have a family. We've got two boys, now middle aged men.

TB: You are still active.

MJ: I try, yes.

TB: Thank you very much for sharing all of this information with us.

MJ: Well, thank you.

35. DILIP V. JESTE

TB: This will be an interview with Dr. Dilip Jeste³⁷ for the archives of the American College of Neuropsychopharmacology. We are in Hawaii at the 40th anniversary of the College. It is December 13, 2001. I am Thomas Ban. Could you just tell us where and when you were born and something about your early interests, education, and training?

DJ: First of all, I want to thank you for this interview. I come from India, where I was born in a place named Pimpalgaon, a small town in the state of Bombay, now called Maharashtra. I was brought up in Poona, which is about 100 miles from the city of Bombay. My father was a judge and my mother was a housewife. I was the fourth out of five siblings. I also went to medical school in Poona. As a teenager, I enjoyed reading Freud, who I found inspiring, especially *The Interpretation of Dreams*, *Everyday Errors of Life*, and *Psychology of Neuroses*. Before going to medical school, I had decided that I wanted to go into psychiatry. So I never saw myself primarily becoming a physician other than a psychiatrist. After I graduated from medical school, I moved to Bombay, which is a much larger city with more academic psychiatry. I was fortunate to work with Dr. Vahia, one of the pioneers of psychiatry in India. He spent a couple of years of his early professional life in the USA and had a strong interest³⁷ in research.

TB: Who was your professor of psychiatry in medical school?

DJ: Dr. Roshan Master was the head of psychiatry. At that time, the psychiatry rotation was six weeks at the B. J. Medical College and Sassoon Hospital in Poona. I found it interesting but not exactly to my liking. Clinical psychiatry was not what I wanted to do. It was not academic.

TB: What kind of psychiatry was it?

DJ: It was essentially pharmacologic and other somatic treatments, especially ECT. The patients were often from villages; they came to the city for treatment when they had psychotic episodes

³⁷ Dilip Jeste was born in Pimpalgaon, India in 1944. He went to medical school at B. J. Medical College in Poona, India. He trained in psychiatry and was first appointed to the faculty at GS Medical College and King Edward Memorial Hospital in Bombay. He completed his residency in psychiatry again in the U.S. at New Jersey Medical College of Medicine and Dentistry and at Cornell Medical School, Westchester Division, before research training at the Intramural Research Program of NIMH at St. Elizabeth's Hospital combined with residency training in neurology. He then joined the faculty of the Department of Psychiatry at the University of California in San Diego. He was interviewed in Waikoloa, Hawaii on December 13, 2001.

and did not have money for medications. They would get some ECT to control them and then would go back to their villages.

TB: But you still wanted to become a psychiatrist?

DJ: Correct, but because of the clinical psychiatry I saw in medical school, I wanted exposure to academic psychiatry.

TB: So, you were ready to do a residency in psychiatry?

DJ: Yes, I went to Bombay, and met Dr. Vahia at GS Medical College and King Edward Memorial (KEM) Hospital. It was the best hospital and medical school in Bombay. Of course I am biased. My wife went to another medical school in Bombay, Grant Medical College, and she maintains that was the best medical school! What I found really exciting was the research perspective. Dr. Vahia was a famous person in India and patients flocked to see him. Yet, he always made it a point to go to the library every day. As residents, we had to read whatever was being published. Whenever we discussed a patient, we had to look for articles on the topic, and this was really unusual for a country like India. There were so many patients to be seen in a short time and not enough psychiatrists. Yet Dr. Vahia emphasized research, and I felt that was what I wanted to do.

TB: What year was that?

DJ: I was in KEM hospital from 1968 to 1974. From 1968 to 1971, I was a resident, and then I was on the faculty. Interestingly, Dr. Vahia's interest was in yoga therapy, but not in the yoga we practice in the United States. It wasn't yoga exercise or relaxation, but personality integration. What he called psychophysiological therapy, which was used for people with psychosomatic disorders such as hypertension. The treatment was based on the concepts of an old Indian sage named Patanjali. Dr. Vahia showed that it had significant physiologic effects such as lowering blood pressure. The result, were published in the *American Journal of Psychotherapy*.

TB: What year?

DJ: In 1973.

TB: Wasn't this your first paper?

DJ: This was one of my first papers.

TB: What was your first paper?

DJ: It was a review on "Hysteria and its Management," published, in 1969, in the *Indian Journal of Medical Sciences*. I was the second of two authors. I also worked with Drs. Doongaji, Bagadia,

and Shah. They were quite sophisticated investigators, and we conducted epidemiologic and treatment studies of schizophrenia, depression, and epilepsy. In India you could easily study 400 or more patients with a given disorder in a short time because we saw over 50 patients a day in our outpatient clinic. Those studies were mostly descriptive, as all we could do was collect demographic and clinical data. Anything more than that, for example biological data or longitudinal follow up, was very difficult. We also did treatment studies. For instance, we compared unilateral with bilateral ECT in patients with schizophrenia; that paper was published in the *British Journal of Psychiatry*. We also conducted research on educational measures, such as testing with multiple-choice questions, which was unheard of at that time. In India you could not be a full time researcher. There were only part time jobs in the university; so, faculty had to be in private practice too. I did well in private practice, but that was not what I wanted. I only wanted to be a researcher and that was not possible due to lack of financial support.

TB: The doctors had their office somewhere in the city outside of the hospital?

DJ: Right.

TB: So, during the mornings you were at KEM, and during the afternoon you practiced in your office?

DJ: Yes.

TB: Alone, or in a group?

DJ: It was a solo practice. I remember the first time I saw a patient and the patient paid me money, I just could not bring myself to accept it. I did not feel that I deserved to be paid. I felt guilty asking for money. Before long, I was getting more patients than I could handle, and I was happy I could do something clinically, but my heart was in research, and I found I couldn't do both. For a country like India, it doesn't make sense to spend money on research, when there are more pressing needs. I realized I needed to go somewhere I could do research. At that time, and even now, the U.S. is the country for conducting full-time research. I knew something about American culture. We read American, British, and Canadian textbooks and, of course, movies, novels, and magazines like *Time* and *Reader's Digest*. My brother was in the U.S. and he sponsored me for my green card. I was accepted for residency by applying without going for interviews after I got my ECFMG. I completed the first year of my psychiatry residency at the New Jersey Medical College of Medicine and Dentistry. It was a very interesting experience. I thought I knew the

culture, and yet it was a shock. A culture shock in terms of psychiatry, too. I was amazed at the dosages of medications compared to those we used in India. For example, if you gave 2 mg of haloperidol to an Indian patient, the Indian patient would be stiff as a board and have marked sedation. In America, I found that we could give 20-30 or even 50 mg of haloperidol and see practically no side effects. Of course, there is a difference between Americans and Indians in average body weight, but it did not fully account for the difference in dosages. I believe that there is a differential pharmacogenetic response to medications and I found that interesting. At the same time, the New Jersey Medical School was very clinically oriented with little research.

TB: Who was the chairman of the department?

DJ: Dr. Thomas. He had done some important work in minority training. One of the nice things that happened in New Jersey was that I met George Alexopoulos, and we became close friends. I also did a small study of tardive dyskinesia in New Jersey.

TB: So almost immediately after you arrived, you became involved in research?

DJ: Yes.

TB: Was this in the mid-1970s?

DJ: July 1974. It was a very simple study. We compared three times daily with once daily administration of antipsychotics in patients with tardive dyskinesia and found that the movements were better suppressed with multiple daily administrations. This was nothing great, but useful and interesting. And it did get published. I also studied the evolution of psychiatric treatments and the role of serendipity in biological psychiatry, although I did not complete that work in New Jersey. I realized I needed to find some place else to conduct research, so I spent my second and third years of residency at Cornell, Westchester Division. Bob Michels was the Chair of psychiatry and Lomy Feder was the Medical Director at the New York Hospital, in White Plains. That was a wonderful experience.

TB: In which journal was your first paper in the U.S. published?

DJ: The first paper was published in *Diseases of the Nervous System*. It was based on the work I did in the first year of my training in New Jersey. I think it came out, in 1977.

TB: You continued your research at Cornell?

DJ: Right. I was always interested in biological psychiatry, particularly neuropsychopharmacology, but Cornell at that time was very psychotherapy oriented. I found it

enlightening, although I knew it was not something that I was going to practice later. I think it made me a better psychiatrist when I learned the principles of psychoanalysis and psychodynamics. In my last year of residency, I did something very different and worked with Jerry Smith, who was the Director of the Bourne Research Lab. I became involved for the first time in animal research. We conducted studies of a stereotactic infusion into the cerebral ventricles, looking at the effects of catecholaminergic activity on behavior in rats. It taught me a lot and made me a better researcher, although I knew that was not something I was going to do for the rest of my life. I have always liked history, so I worked some more on the serendipity paper. Cornell had a great department of History of Behavioral Sciences. I also wrote a paper there on the history of schizophrenia. That paper challenged an existing notion of schizophrenia. It is usually taught that schizophrenia is a disease of civilization, which appeared 100 to 200 years ago. What we found was that schizophrenia is probably as old as mankind. There is something called the Poem of a Righteous Sufferer, which may be the first description of a paranoid person, maybe paranoid schizophrenia, on the cuneiform tablets from the Mesopotamian culture, representing the oldest human writings. Of course, we cannot diagnose schizophrenia in ancient writings using DSM criteria. But going through that as well as some descriptions from medieval times, and a number of later writings, we provided examples of what looked like schizophrenia throughout human history.

TB: Did you try to differentiate schizophrenia from delusional psychosis and manic depressive psychosis?

DJ: The differential diagnosis of people in old literature can be very difficult. At the same time, there are some features that seem to be strongly suggestive of schizophrenia. There was a description in Indian Rigveda, written a couple of thousand years before Christ, of a young person with “insanity.” It looked like there were people who had psychotic symptoms without obvious evidence of bipolar disorder. I believe that schizophrenia is not a disease of civilization but a biological disorder present from the beginning of human history. I think the incidence and prevalence have varied depending on environmental factors.

TB: So you did some work on the history of psychiatry.

DJ: In addition to a great Department of History of Behavioral Sciences, Cornell owned several ancient books which were a dream. I always liked reading. Even as a kid going to the library and

getting books was my passion. The history research at Cornell was exciting because I found some fascinating old literature and was able to interpret it in a new way. It was intellectually challenging.

TB: Did you publish your research on the pre-history of schizophrenia?

DJ: Yes.

TB: Where was it published?

DJ: In *Comprehensive Psychiatry*. But the study I mentioned earlier on tardive dyskinesia, influenced my career the most because it challenged the conventional wisdom of the time and was published in the *Archives of General Psychiatry*, after I moved to the NIMH. The ACNP Task Force report, in 1972, had suggested that tardive dyskinesia was the result of long-term neuroleptic treatment and that stopping treatment from time to time, so called “drug holidays,” might prevent its occurrence. We found that stopping treatment not only increased the risk of relapse in schizophrenia but intermittent treatment also seemed more likely to be associated with tardive dyskinesia. It was a cross sectional study, so we could not establish causality, but the findings led to a long discussion in the field and over the years people began to accept our conclusion. Years later, John Kane, in a longitudinal study, confirmed the finding. This was one of two papers that were published in the *Archives* at nearly the same time. The other was on serendipity in the discovery of psychiatric treatments.

TB: So you published on serendipity in the discovery of psychiatric treatments?

DJ: That research was done at the Cornell History of Behavioral Sciences Department. The word serendipity relates to ancient Ceylon or Sri Lanka (Serendip), where the anti-malarial properties of quinine were accidentally discovered. But we found that most discoveries in biological psychiatry were not really serendipitous. The discoverers did not know what they were going to find, but they were looking for something. Let’s take the example of malaria therapy. Wagner von Jauregg got the Nobel Prize for malaria therapy in cerebral syphilis. He found that people with syphilis, who had malaria, were less likely to have psychosis. This led to the idea that if you induced malaria it could improve or prevent psychosis due to schizophrenia. At that time, this made sense because there was no other effective therapy for schizophrenia.

Let’s take one of the more recent discoveries of antidepressant effects of antituberculosis medications such as iproniazid.

TB: Nathan Kline’s discovery?

DJ: Right. He and others found that patients with tuberculosis treated with drugs like iproniazid showed improvement in depression, so they tried the drug in depressed people without tuberculosis. At the time, they did not know about monoamine oxidase. However, they were smart enough to put two and two together and come to the correct conclusion.

TB: And they discovered the antidepressant effect of iproniazid.

DJ: Correct. Another example would be the neuroleptics. These drugs were used by anesthesiologists and surgeons who found that sedative and antihistaminic “lytic cocktails” calmed patients before surgery. The thinking then was that you could use these drugs to calm psychotic patients. You could argue that it was not a scientific or logical discovery because they did not know the drugs blocked dopamine receptors. There is also the discovery of lithium, which is often given as an example of basic science research leading to clinical discovery. Cade, a practicing Australian physician with a basic science laboratory, found that lithium had a sedating effect on animals.

TB: You are implying that serendipity is not enough.

DJ: The point is that scientific discoveries are not usually a pure accident. There is some luck, but luck alone does not help unless you have the potential and ability to use it. Only Newton came to the conclusion that gravity caused an apple to fall from a tree. Others saw apples fall from trees but did not discover gravity. I believe that science involves lots of work and that you need to be looking for something relevant. Of course if you knew exactly what you were looking for, it would not be a discovery. I remember there was a book on *Discoveries in Biological Psychiatry*. I thought you contributed to it.

TB: I didn't. Frank Ayd and Barry Blackwell published that book.

DJ: Anyway, I had those two papers, on tardive dyskinesia and on serendipity published at about the same time in the *Archives of General Psychiatry*. Those are still two of my favorite papers. At Cornell, I applied for and was selected for a research fellowship at NIMH. This had been my dream when I was in India. I wanted to go to NIMH because everybody knew it was the place to learn and conduct research. I was dreaming about something I had never seen.

TB: So you went to the NIMH?

DJ: Yes. At Cornell I found that learning new things really turned me on. I was doing dynamically oriented psychotherapy with borderline patients, going through the history books, working with

animals or conducting clinical research. Cognitively, it comes to the same thing - the excitement of learning something new. That is what turns me on.

TB: When did you go to NIMH?

DJ: 1977. I was there for nine years and worked with Richard Wyatt in the neuropsychiatry branch at St. Elizabeths' Hospital along with Floyd Bloom, Ermino Costa, the basic scientist, and Chris Gillin.

TB: It had to be very stimulating.

DJ: It was. I could not believe that people were paying me to learn and conduct research. I thought I should pay them! The National Library of Medicine at NIH was the largest in the world. I felt like a kid in Toys 'R' Us. That is the fascination of NIH; there is an expert in every area and so many topics to explore.

TB: That must have been a great experience for you given your interests and expectations. DJ: Yes, Richard Wyatt was my supervisor, and he was very good. He let me do a lot of different things. I conducted clinical research, did some animal research, and worked in neurochemistry labs. I found it helpful to explore different things and find out what suited me most. One of the first things I did was to write a book on tardive dyskinesia. It was during the fellowship and I spent about a year doing it. This was not an edited book and it was about 250 pages long, so I had to teach myself neurochemistry and neuroanatomy in order to write it. It was the first book I published and I still think it is the best book on tardive dyskinesia. Richard Wyatt was the second author. Ross Baldessarini reviewed the book, and did a great job helping me take the subject further. I found it a tremendous experience. I also worked on the neurochemistry of schizophrenia, especially paranoid schizophrenia. I performed some neuropathology studies and did some collaborative research with people in India. I am proud to be an American citizen but also proud to have come from India. On one trip I went back to India and collected spinal fluid from a group of hospitalized patients with tardive dyskinesia to take back to NIMH and look at the levels of norepinephrine. I felt that the dopamine receptor supersensitivity theory of tardive dyskinesia had been overblown, and that it was not the explanation for tardive dyskinesia. I thought there were other mechanisms with increased catecholaminergic activity that were critical. In this study, we found that was the case; there was an increased level of norepinephrine metabolites in patients with tardive dyskinesia compared to controls. We published that in the *British Journal of*

Psychiatry. An interesting aspect of that study was that the Indian customs would not allow people to take biological fluids out of India. They did not want blood to be sold or misused. Even a tiny amount of cerebrospinal fluid could not be transported, so we did something which we might not have been allowed to. But I feel it was the only way to study the biology of tardive dyskinesia in India, using American technology and expertise. Tardive dyskinesia is less common in India, but the neuroleptic dosages are also much lower. One of the fringe benefits of being at NIMH was that I completed the two remaining years of my neurology residency while I was conducting research in the evenings and on weekends. That was also the time my wife, who is a child psychiatrist, had our second daughter. So, it was a really busy period, but I found that it was helpful being a neurologist. It made me much more knowledgeable about medicine. I published almost a hundred papers while at NIMH.

TB: Did you publish exclusively on your findings in schizophrenia?

DJ: Not exclusively, but a number of the papers were on schizophrenia. One paper I should mention, which I worked on with several of my colleagues, won the A. E. Bennett Award from the Society of Biological Psychiatry. It was on heterogeneity in schizophrenia from a biological viewpoint. We noted that schizophrenia is usually classified on the basis of clinical symptoms as paranoid, hebephrenic, or catatonic. It did not make much sense because, except for the paranoid type, the others are not biologically distinct. So, we looked at different dimensions for grouping people with schizophrenia. One dimension was tardive dyskinesia. One was size of the ventricles on CT, large versus small. Another was neurochemical, and so on. That was what we called “*ex uno multi*,” which means many out of one. It is the opposite of “*e pluribus unum*,” which means one out of many. It is not that there are different types of schizophrenia, but there are dimensions. These are not distinct subtypes that you can divide patients into, rather they are dimensions.

TB: So again, what are the different dimensions?

DJ: Ventricle size, tardive dyskinesia, paranoid schizophrenia, neurochemical, and cognitive changes.

TB: Negative symptoms?

DJ: There could be a dimension of negative symptoms. An individual patient could be categorized according to all of those dimensions.

TB: One of the dimensions you mentioned was tardive dyskinesia. Some patients develop tardive dyskinesia, others don't. DJ: Right.

TB: Is there any way of predicting who will not develop it?

DJ: I think there are people who would not develop dyskinesia even if you treated them for 100 years. We saw patients in St. Elizabeth's Hospital who were being treated with high dosages for 30 years but did not have one symptom of dyskinesia. On the other hand, there were patients treated for six months who developed severe dyskinesia. So susceptibility to tardive dyskinesia is an important dimension.

TB: And you have the other dimensions.

DJ: It is a multidimensional concept. For example, somebody with schizophrenia who has large ventricles and severe negative symptoms would be susceptible to tardive dyskinesia but that might not solely explain the risk. There might be something else that we do not yet know about dyskinesia. So, while our results were interesting, more important was the approach. We should not divide people into specific subtypes such as type I and type II but look at them in terms of different dimensions and how much of each dimension a person has. That was the approach we took to understanding the heterogeneity of schizophrenia. A patient could be rated on each dimension, say 30% susceptible to tardive dyskinesia, 40% in terms of ventricles, etc. Saying that schizophrenia has multiple dimensions is better than saying that there are fixed subtypes, which is usually how schizophrenia is conceptualized.

TB: Do you think that schizophrenia is a valid diagnostic concept or it should be broken up?

DJ: My view is that chronic psychosis is the syndrome. In maybe a decade or more, chronic psychosis will be identified as a syndrome, when we find something unique biologically about it. I do not think schizophrenia is necessarily a unique disorder and that schizophrenia, psychotic mood disorders, delusional disorder, and psychosis not otherwise specified, are all probably more similar than different biologically. Right now, we differentiate all these disorders on the basis of clinical symptoms. I think that is not going to stand the test of biology. I expect we will identify genes for mood disorders, and genes for psychotic disorders. Within psychotic disorders, we will have subgroups which may be more dimensional than categorical. For example, if you have an equal number of genes for schizophrenia and for depression, you will have a psychotic mood disorder. If you have multiple genes for schizophrenia and only one or two for mood disorder, you

may have schizophrenia with mild depression. Something like that. Right now we are focusing so much on dividing schizophrenia into clinical subtypes, and then separating schizophrenia from psychotic mood disorders, and so on. I do not think that will stand the test of time. We will have chronic psychotic disorder as a syndrome that includes schizophrenia as well as psychosis with depression or other disorders.

TB: What are the symptoms of chronic psychotic disorder?

DJ: The symptoms could be delusions, hallucinations, and thought disorder. Actually cognitive impairment would be present in all of these patients, not the type of cognitive impairment we see in dementia, but cognitive impairment in terms of learning and executive function. Many patients will also have some negative symptoms.

TB: Such as?

DJ: Negative symptoms such as flattening or blunting of affect, social isolation, social withdrawal, alogia. So, the patients would have some positive symptoms such as delusions and hallucinations and some negative symptoms plus cognitive impairment. There would be differential response to antipsychotics. Only the positive symptoms would show significant improvement.

TB: Are these patients distinctly different from patients with mood disorders?

DJ: Yes. One important differentiating factor would be the usual age of onset of illness, something I became interested in when I left NIMH.

TB: Where did you move?

DJ: After I was at NIMH for a number of years, I decided that I needed to move on and do something on my own, so I looked at different places. At the University of California in San Diego (UCSD), I found exactly the type of place I wanted, and so I moved there. It was partly by serendipity, though not entirely so, that I got into geriatric psychiatry; UCSD had an opening in geriatric psychiatry. They were just starting a program and wanted me to be its Director, although I did not see myself as a geriatric psychiatrist, at that time. However, I had a wonderful fellow by the name of Jackelyn Harris. Once I decided I was going to run a geriatric psychiatry program with my research background being in schizophrenia, it seemed to make sense to focus on schizophrenia in older people. Again, it was exciting, something new that very few people had studied before. I found out how little was known in this area, especially in the United States. There was a long tradition of geriatric psychiatry in Europe, and a lot of work on paraphrenia for example. Canada

also had a number of excellent studies done on paraphrenia and late-onset schizophrenia. In the United States, on the other hand, there was very little published on the topic. DSM-III, which came out in 1980, said that you could not diagnose schizophrenia when the onset of psychotic symptoms was after age 45. So, I wanted to study people whose illness looked like schizophrenia but with an onset after 45.

TB: So your interest turned to late onset schizophrenia?

DJ: I found that challenging, so I started with a literature review; there was very little and yet people had strong biases. Then we collected a sample of patients who had what looked like schizophrenia but with an onset after age 45. Most researchers did not believe there was such a thing as late-onset schizophrenia. We studied those patients with a grant from NIMH, the first I received. We performed extensive clinical evaluations and conducted comprehensive neuropsychological studies.

TB: In what year did you get the grant?

DJ: In 1987. It became a ten-year grant after I received the NIMH merit award. That was a wonderful experience. As I got more and more into it, the whole field became fascinating. Now, I identify myself, first, as a geriatric psychiatrist, something which I never would have thought of until I moved to San Diego.

TB: But didn't you still continue your research in schizophrenia?

DJ: Yes. My work is still primarily on schizophrenia and aging. I find that there are two exciting parts to this; one is late onset schizophrenia, and the second is what happens to early onset patients as they get older. I find the concept of dementia praecox wrong; schizophrenia in older people is neither dementia nor is it necessarily "praecox"; it can have late onset.

TB: Didn't Kraepelin adopt the terms from Morel via Kahlbaum?

DJ: Yes, that is true. He described paraphrenia in later life. However, he still believed that paraphrenia was a different illness from dementia praecox, and that these were people whose course was more benign than dementia praecox. On the other hand, Kraepelin's students who followed his patients found that the course of paraphrenia was generally similar to that of dementia praecox. Still, if you talk to most researchers in schizophrenia, they think it is dementia praecox, although they don't use that term. When DSM-III changed to DSM-III-R, it removed the restriction on age of onset. But there remains a fair amount of skepticism about onset of schizophrenia after

45, and similar doubt about possible remission of schizophrenia. The concept of schizophrenia as dementia persists - not Alzheimer-type dementia, but a neurodegenerative disease. The concept of schizophrenia is a life-long illness; once you have schizophrenia you will always have schizophrenia. I find that a fallacy. In many cases, schizophrenia is a life-long illness, but there are a proportion of patients who I believe have a true remission. I find that in late-onset schizophrenia, remission is not common. Nonetheless, our understanding of these conditions has the potential of revolutionizing treatment in two ways. I see late-onset schizophrenia as nature's experiment for delaying onset of the condition. While most people who have schizophrenia develop the illness between 15 and 25 years of age, some people are protected from developing it until age of 50 to 55. If you could identify factors that lead to delay in the development of illness, modify them, and slow the onset of schizophrenia from early life to the 50s, the improved quality of life would be tremendous. That is something I believe we need to do.

TB: On what basis do you imply that it's schizophrenia?

DJ: Good question. How would you know somebody has schizophrenia? You can't look at the brain and make the diagnosis. So, what we call late-onset schizophrenia are patients who meet all of the usual criteria for schizophrenia and would not meet criteria for any other major DSM disorder. We have followed these patients longitudinally, some for over ten years. These patients are evaluated every year and continue to meet the criteria for schizophrenia. They are treated just like other patients with schizophrenia, except for lower dosages of antipsychotics. The concept of late-onset schizophrenia is well accepted in other countries. Last year, we published a paper in the *American Journal of Psychiatry* on, "The International Consensus Statement on Late-onset Schizophrenia." There were people from a dozen different countries, including Robert Howard, Mary Seeman from Canada, Peter Rabins, and myself.

TB: So, Mary Seeman was also involved in this area of research?

DJ: Mary has done some great work in older people with schizophrenia and estrogen especially. Anyway, we published the consensus paper, in which we said we believe in late onset schizophrenia, and that it is different from early-onset illness in some ways. Gender is a big difference. It is much more common in women, while early-onset schizophrenia is much more common in men. That may give us some clue about estrogen or something related to it as a possible protective factor; I think it is simplistic to say that it is only estrogen. But to answer your question,

I do think it is schizophrenia, but schizophrenia is a broad, heterogeneous entity. Obviously, not all people with schizophrenia are similar. There are different subgroups. Patients with early-onset and late-onset schizophrenia are different in some ways. However, they are also similar in many ways. What we need to do is find out what protects some people from developing schizophrenia until later in life. Most Alzheimer's patients develop dementia at 65, but some people get it at the age of 40. These are not only people with Down's syndrome, but also people homozygous for the APO-E4 gene. I think we will find genetic and other markers that could be associated with late-onset schizophrenia. It could be some neurochemical abnormality or a unique psychosocial factor. We need to find those to help us delay the onset, and even, in the long term, prevent schizophrenia. The other side of the coin is remission of schizophrenia in old age; that too, is a controversial concept. Most researchers think that there is no such thing as remission of schizophrenia. If you read the older studies of Manfred Bleuler, he described patients with schizophrenia who after decades of institutionalization, began to improve and function well. That is one area that we have been looking at. We published a case of a patient we had been following longitudinally, who had schizophrenia, and subsequently, went into a persistent remission. The point is that there is a small minority of people who seem to have a true remission of schizophrenia. We need to study those patients well and find what causes remission because if we identify those factors and modify them, a cure of schizophrenia would be possible. Right now, to talk about prevention or cure of schizophrenia is heretical. TB: As you know, it has been proposed by some to split schizophrenia into two classes of disease. What are your thoughts about that?

DJ: I personally do not think you can split them into two groups, however, I think a very important dimension I would use is age of onset.

TB: In terms of age of onset, doesn't paranoid schizophrenia have a later onset than the other forms?

DJ: Are you talking about paranoid schizophrenia or paraphrenia?

TB: Paranoid schizophrenia.

DJ: Paranoid schizophrenia does tend to have a later age of onset than non-paranoid schizophrenia. In terms of paraphrenia, Kraepelin did not use age of onset as a differentiating criterion. The distinction was only made later, when Sir Martin Roth, one of the pioneers in geriatric psychiatry, reported on paraphrenia and late paraphrenia, the latter being after age 65.

TB: But you do separate that late-onset group from the others?

DJ: Yes. Late and early onset schizophrenia are different. However, I personally do not think there is any fixed age cut off that one should use rigidly to differentiate. This is not just true for schizophrenia but also applies to other disorders in the chronic psychotic syndrome, including psychotic mood disorders, psychosis not otherwise specified, etc. All of them have different dimensions on which they can be subtyped, and one of the really important dimensions would be age of onset of the psychotic syndrome. However, it wouldn't be a fixed age cut off. Kraepelin was right about differentiating mood disorder and schizophrenia, but the differentiation would not be so much in terms of the course, which he used for this purpose. I believe that schizophrenia is not necessarily a continuous life-long illness, and, at the same time, mood disorders are not necessarily episodic. Recent work on minor depression shows that it can be very common in between episodes of major depression.

TB: It seems that you are in agreement with Leonhard's classification.

DJ: Was he the one who called it process schizophrenia versus reactive schizophrenia?

TB: No, he was the one who separated unsystematic from systematic schizophrenia. Unsystematic schizophrenia is episodic, whereas systematic schizophrenia is continuous. Are you doing any research in this direction?

DJ: What we are now focusing on are mainly middle aged and elderly people with psychotic disorders. We have a NIMH funded Center to look at that. We study schizophrenia, delusional disorders, and psychotic mood disorder. TB: Just late-onset psychotic disorder?

DJ: No, not just late-onset. These are people who are currently middle aged or elderly; the majority, had onset in early life but are getting older. We take anybody over 40 and there is no upper age limit. In my next few years I want to focus on the geriatric patient population, over age 65, because that is the population that has been understudied over the years, the elderly psychotic patients. Yet that population is going to increase tremendously.

TB: Could you elaborate on this project?

DJ: We do longitudinal studies of psychopathology, neuropsychological performance, and motor function, but in the last few years, we have moved into intervention research. We are doing studies of not just pharmacologic treatments, but also psychosocial interventions, like combined cognitive behavior therapy and social skills training.

TB: Are you comparing the effects of different treatments?

DJ: Almost everybody needs antipsychotics in this group, so what we do is study the effects of antipsychotics plus cognitive behavioral and social skills training. Antipsychotics, alone, would not necessarily improve patients' functioning. In the last few years, the focus has been more and more on psychosocial treatments, and much less on neurochemistry, because I don't have the right type of neurochemical markers to look at. I am at the stage in my life where I want to do something to help patients directly. While understanding the illness is important, how can we really help them? We assess the patients at baseline, and there are different treatment protocols. Just about all of these are federally funded research studies, but some are long term treatments for nine months. Let me give one example. We are comparing three different atypical antipsychotics, risperidone, olanzapine, and quetiapine in middle aged and older patients with psychotic disorders, looking at the therapeutic and side effects, not just dyskinesia. Tardive dyskinesia is much less common with this new class of drugs than with the older drugs, but we have new tardive disorders. In other words, it is not tardive dyskinesia, but new long-term side effects, like diabetes, weight gain, and who knows what others. It took 10 years after neuroleptics were introduced into psychiatry before tardive dyskinesia was reported, five years actually to be perfectly correct, but 10 years before people really became aware of it. Most of the newer drugs have not been out that long. So, we may still see something in the years to come. Another study is headed by a young faculty member, Laurie Lindamer. She is looking at the effects of estrogen in postmenopausal women with schizophrenia. A couple of psychologists in our group have studies of combined cognitive behavioral therapy and social skills training in older people with schizophrenia. One study we have not started yet, but I am excited about, will look at work rehabilitation in older people with schizophrenia. A number of studies have shown that in a younger population it works very well, though not in everybody. In the case of older patients, there is rampant ageism, so it is important to show that older patients can work too, if they are provided with appropriate help and training.

TB: What would you consider your most important contributions to the field of neuropsychopharmacology?

DJ: Only time can tell, but what I find most exciting is the work on aging and schizophrenia both in terms of age of onset and remission. It has the potential for markedly improving our understanding of schizophrenia, in general.

TB: What about your early work on tardive dyskinesia?

DJ: It was a really useful experience in terms of learning research and helpful in showing that there is something called tardive dyskinesia. When I started working in that area, many people did not accept its existence. In the late 1970's, there was a paper in the *Journal of Clinical Psychiatry* titled, "Tardive Dyskinesia: A Myth?" Even in the 1980s, there were papers in journals like the *Archives* that said there was no such thing as tardive dyskinesia in patients with schizophrenia.

TB: What would you consider your most important publication?

DJ: The papers on tardive dyskinesia were important because they brought attention to tardive dyskinesia, and also showed how it was different from what many people thought. Another is the paper on late-onset schizophrenia. I think my best paper is yet to be written. One paper I want to write would crystallize my thinking on schizophrenia and aging. I am considering a new book in the next few years on aging and mental illness.

TB: What was your last publication?

DJ: The very last paper that I published was on psychosis in Alzheimer's disease. If you are asking about a database paper, there are several that came out around the same time.

TB: Just the one you think is the most important.

DJ: Not necessarily a paper that I am the first author on?

TB: Not necessarily.

DJ: Two such papers came out recently. One, in the *Archives of General Psychiatry* was a longitudinal study of schizophrenic patients with cognitive assessments on an annual basis. That was one of the most comprehensive papers on stability of cognitive deficits in older people with schizophrenia.

TB: When did you become a member of ACNP?

DJ: A long time back. I do not remember the year; it was the early 1980s, maybe 1983, or so. I was very fortunate to be selected a member the first time I applied. The ACNP is a wonderful organization. It makes you very humble because you see how smart other ACNP members are.

TB: Am I correct that you are the president of a new organization?

DJ: Yes. I wanted something that was like ACNP, but international, and focusing on geriatric Psychiatry. So, we founded the International College of Geriatric Psychoneuropharmacology, (ICGP).

TB: Aren't you also the editor of a journal?

DJ: Yes. This is *The American Journal of Geriatric Psychiatry*.

TB: Is there anything we left out and you would like to mention?

DJ: I find the field of geriatric psychiatry extremely fascinating and important. In the next 30 years, growth of the elderly population is going to be tremendous. I hope that I can do something to help them.

TB: On this note we should conclude this interview with Dr. Jeste. Thank you for sharing this information with us.

DJ: Thank you.

36. JOHN M. KANE

TB: This is an interview with Dr. John Kane³⁸ for the archives of the American College of Neuropsychopharmacology. We are in Acapulco, Mexico; it is December 11, 1999. I am Thomas Ban. Let us start from the beginning; when and where were you born? Tell us about your education and how you got involved in research in psychopharmacology.

JK: I was born in New York City in 1945 and grew up in suburban Westchester County. My father was a physician and my mother was a buyer for the Army and Air Force Exchange Service. My father specialized in pulmonary medicine and was very influential in my decision to go into medicine. He had enormous intellectual curiosity in a variety of areas and made significant contributions to X-ray techniques and pulmonary medicine. I went to high school at the Horace Mann School in New York and attended Cornell University, where I majored in English. From there I went to NYU Medical School and became increasingly interested in psychiatry, spending a good deal of elective time working on different projects. One of these was with Neal Miller at Rockefeller University, another with Stella Chess in the Child and Adolescent Psychiatry Department at NYU, and a third involved evaluating the Substance Abuse Treatment Program in a residential community model. Those experiences were very valuable in forming my subsequent decisions and perspectives. TB: Where did you do your residency in psychiatry?

JK: I did my psychiatric training at Hillside Hospital and the reason, primarily, was that as a medical student, wandering around the bookstore and library, I came across a book Don Klein and John Davis had published in 1969 on Psychiatric Diagnosis and Treatment that made a profound impact. I have kept my original, underlined, annotated copy, which I started reading in medical school. Don Klein was at Hillside and that was an important factor in my decision to choose it for residency.

TB: Are we in the late 1960s?

JK: Right. The book was published in 1969. I graduated from medical school in 1971 and spent four years doing residency at Hillside Hospital. During residency, I tried to fulfill a dream I had

³⁸ John M. Kane was born in New York City, New York in 1945. He received his M.D. from New York University Medical School in New York City, New York. He completed his psychiatric residency at Zucker Hillside Hospital in New York, where he subsequently joined the faculty of the Department of Psychiatry at the Hofstra-North Shore Long Island Jewish School of Medicine. He was interviewed in Acapulco, Mexico on December 11, 1999.

to spend time studying anthropology and sociology. So I took graduate courses at Columbia in those departments, and they were very helpful in giving me a broader perspective on factors that influence human behavior. During residency, I started working with Don Klein and Rachel Gittelman-Klein in research and I'm very grateful to Don for making himself available to me as a resident. He would let me sit in on his consultations with private patients as an observer to learn from his diagnostic and treatment approach; needless to say that was a very valuable experience. Don Klein has been one of the most valuable contributors, helping to advance the field in terms of diagnostic sub-types and response to pharmacologic agents. Having that perspective as a resident was extremely valuable and made me more and more interested in research. So when I finished residency, in 1975, I began working full time in research, not only with Don, but also with Arthur Rifkin and Fred Quitkin; they also were extremely generous. They treated me as a peer rather than a resident and made me feel I was an equal member of the team. Beginning to spend full time in research in 1976, with another colleague I started the Lithium Clinic at Hillside Hospital. We did a number of very large treatment studies in unipolar and bipolar depression, subsequently, published in the *Archives of General Psychiatry*. A lot of that research was done under the leadership and guidance of Fred Quitkin, Arthur Rifkin and Don Klein. So, during the first couple of years of my residency, I was heavily involved in affective disorders, particularly bipolar disease, becoming an expert in the management of those patients. We ran over a hundred and fifty patients through long-term clinical trials, involving lithium, imipramine, and in some cases, placebo. After that, Don and his group were recruited to Albert Einstein by Ed Sachar, and then, to Columbia. I had a choice as to whether to go with them or stay at Hillside. That was probably one of the more difficult career decisions I ever made, because I knew I was not ready to go it alone. Don Klein made the decision easier by telling me if things didn't work out at Hillside I would be able to move to Columbia. For the next year or two I continued to meet, quite frequently, with Fred Quitkin, Art Rifkin, and Don to get their advice, but within a couple of years, I was able to get my first NIMH grant, examining the dose response relationship in long term maintenance treatment. The idea was of using antipsychotic drugs to prevent relapse in patients with schizophrenia. We did some pilot studies first, which suggested that extremely low doses of antipsychotic medication could be effective and then set up a large controlled trial, which involved about one hundred and sixty patients.

TB: When you say, extremely low doses of antipsychotic medications could be effective, what do you mean?

JK: Fluphenazine decanoate, 1.25 to 5 milligrams every other week. At that point in time, there had not been a lot of work on trying to establish minimum effective doses for maintenance treatment. One of the incentives was to reduce some of the long-term side effects that had been associated with antipsychotics, specifically, tardive dyskinesia (TD).

TB: So you were interested in reducing the occurrence of TD. Could you tell us something about TD?

JK: TD is a syndrome that was observed shortly after the introduction of antipsychotic drugs, in the mid to late 1950's. It involves abnormal involuntary movements, usually of the mouth, tongue, and face, but often involving the extremities as well. In its most severe form, this could be disfiguring and disabling. In some cases, it was persistent for years even after the antipsychotic drugs were discontinued. Initially, there was debate as to whether or not this condition was due to antipsychotic drugs, but it became clear, over time, that the drugs were playing a major role in causing this condition. A major goal in psychopharmacology, in that era, was to see if we could reduce or eliminate the risk of TD. Our desire to identify minimum effective dosages for maintenance treatment was, to some extent, driven by concern about TD. We did show, using these micro doses, we could produce a significant reduction in the early signs of TD. On the other hand, the risk of relapse did go up on the small doses we used, although the relapses were not usually severe and did not, necessarily, require hospitalization. There was a balance of risk to benefit when one begins to approach the minimum effective dose. We went on to do a number of studies, including participation in a large NIMH funded multi center project, called Treatment Strategies in Schizophrenia in which Hillside was one of five sites. Another area we began work on was first episode schizophrenia. There had been very few studies focusing on that population. We knew antipsychotic drugs were very effective in controlling the acute signs and symptoms of schizophrenia, but it was not clear whether one needs to continue treating patients over a long period of time after recovery from a first episode. In collaboration with Fred Quitkin and Arthur Rifkin, we published a paper from a placebo controlled maintenance trial in first episode patients. We demonstrated there was a significantly higher risk of relapse among patients assigned to placebo than among patients continued on active drug. The trial lasted for a year. The sample size

was relatively small, twenty-eight patients, but we were able to show a significant difference. It was the first controlled trial on maintenance treatment of schizophrenia. In spite of the fact we and others have shown that the relapse rates, after five years, among untreated patients was as high as eighty percent, we are still struggling to get patients to accept continuation of medication after remission from a first episode. The results from the most recent study at Hillside suggest that medication can reduce the risk of relapse by a factor of at least four and is the single most important factor. In our first episode maintenance study, it turned out that patients with poor pre-morbid social adjustment had a much higher rate of relapse when they went off medication than patients who had better social adjustment. In the early 1980's, when I recruited Jeff Lieberman, we continued with studies in first episode patients, following them longitudinally and looking at issues such as brain morphology, cognitive functioning, neuroendocrine response, treatment outcome, relapse, and so forth. In the late seventies there were a couple of other areas we were actively pursuing.

TB: Didn't you continue with your research on TD?

JK: We did. Jim Smith and I wrote a very extensive review on the prevalence of TD, which was published in the *Archives*. It pointed out that the estimates of the prevalence of TD ranged from half of one percent to as high as fifty-six percent. That made it clear there was a lot of uncertainty as to how serious a risk TD really was. So, we decided to start a prospective study of TD. Many people said it was overly ambitious to try to follow patients longitudinally to determine whether they would develop tardive dyskinesia, but we had the necessary population and infrastructure at Hillside. We were also able to win support from NIMH for a very large scale prospective study of TD development, which went on for more than a decade. Findings of our study suggest the incidence of TD grows with cumulative antipsychotic exposure by about five percent annually. We identified some risk factors for developing TD, for example early EPS. We also demonstrated that patients with depression, particularly unipolar depression, were at greater risk for developing TD. There's still a debate about whether bipolar diagnosis is also associated with a higher risk. We did not find that, but we did find that lithium, when given concurrently with antipsychotic drugs, confers some protection against tardive dyskinesia. The rationale for that is lithium's ability to reduce the hypersensitivity of dopamine receptors. That prospective study of TD was rather unusual and did provide very valuable data for both investigators and clinicians.

TB: Could you elaborate on what kind of valuable data it provided for investigators and clinicians?

JK: It provided valuable information, for example, relevant to informed consent. In the area of TD, the simple fact of being able to say that the risk for developing it is five percent over time, is helpful in discussing the risk-benefit ratio of treatment. It was also important feedback to those involved in drug development by underlining the need for compounds that would have a significantly reduced risk for TD.

TB: So this is how you got involved in research with clozapine?

JK: The next area of research we got involved with was with clozapine, a so-called atypical antipsychotic drug, which had been around for a while, but had not been marketed because, in the mid 1970's, there were several fatal cases of agranulocytosis in the course of treatment. As a result, a conclusion was drawn that clozapine appeared to have a significantly higher risk of agranulocytosis than conventional antipsychotic drugs, such as chlorpromazine, which was known to produce agranulocytosis rarely. In the early days of chlorpromazine treatment, people used to do blood tests because of that risk but, subsequently, it was concluded that agranulocytosis was so rare it was not necessary. Clinicians were also aware that patients could recover from agranulocytosis with withdrawal of the original medication and appropriate medical management. When clozapine appeared to have a significantly higher risk of agranulocytosis, its marketing was curtailed, but even in those years, it was available in some countries with the necessary precautions.

TB: How did you actually get involved with clozapine?

JK: In about 1977, I was approached by Sandoz, currently known as Novartis, to take over the management of a group of patients who had been receiving clozapine from Nathan Kline.

TB: So that is how you got involved with clozapine?

JK: We had read about clozapine and felt it did differ from other antipsychotic drugs in its ability to produce a range of clinical effects, which seemed broader than other antipsychotic drugs; it seemed to be helpful in some patients who had not done well on other drugs. The main characteristic of the drug, universally agreed upon, was a very, very low propensity to induce Parkinsonism. That we found very intriguing, because we assumed that drug-induced Parkinsonism was an intrinsic character of all effective antipsychotic medications. Clozapine really set a new standard in that regard. Chemically, it is not that dissimilar from some tricyclic

antidepressants, but it did have novel receptor binding characteristics, in that it bound to a broad array of receptors, including serotonin, alpha adrenergic, and histaminergic receptors, as well as dopamine receptors. At that time, we were aware of the different sub-types of dopamine receptors that clozapine was subsequently shown to bind to. So, it did appear to have a number of novel properties. Also, it did not elevate prolactin and seemed to be more effective in improving negative symptoms, although that was anecdotal at the time. It is relevant to the story that in the late 1970's, we, at Hillside, were one of the few sites in the United States using clozapine.

TB: So, Sandoz contacted you to take over Nate Kline's clozapine treated patients and do what?

JK: What Sandoz wanted was that I try to discontinue clozapine in the patients because there was no IND for clozapine at that time. We took on the challenge but, when we tried to discontinue clozapine in a number of patients, the consequences were unfortunate. I regret having attempted to do that, but we really did not know what to expect. What happened was that the first couple of patients suffered very severe relapses and we had to hospitalize them. We tried numerous other medications, but none seemed to help. So, we put them back on clozapine and both the nurses and attending staff were very impressed with the results. This experience changed my attitude towards the possibility of having a differential response to antipsychotic medications. We had all grown up with the notion that antipsychotic drugs were interchangeable, in terms of clinical effectiveness. There had been about a hundred studies comparing chlorpromazine and trifluoperazine to other drugs in the acute treatment of schizophrenia, and only one out of a hundred studies showed a difference, which is something you can get by chance. So, we assumed the drugs were equally effective in group comparisons; but clozapine seemed to hold the promise this might not be the case. Our experience with the first few patients we took off clozapine had a dramatic effect on me. I became so interested in clozapine that we began to treat some patients, who had failed to respond to other drugs, with it. By the time we had an IND, Sandoz had established the fact that agranulocytosis was generally reversible if the drug was promptly stopped. It was also recognized that, if proper medical management was provided, mortality declined substantially. I thought if it could be shown that clozapine had some unique or superior properties in comparison to the available medications, it would be an important addition to our treatment armamentarium. We had a number of meetings with the Food and Drug Administration about our interest. At the first meeting, we talked about some of the anecdotal data that was available and suggested this drug

might hold promise for some patients with treatment refractory schizophrenia. The decision was that the FDA would consider approving this drug for marketing if, in the context of a prospective well-designed study, we could demonstrate clear superiority over an available control drug. We took on that challenge and I became the lead investigator in designing and implementing a large multi-center study, funded by Sandoz, in hospitalized treatment-refractory patients who had failed multiple other drugs and also failed a prospective trial of six weeks treatment with haloperidol in doses of up to 60 mgs a day. They were patients who had been chronically institutionalized, for whom clinicians and expert psychopharmacologists had nothing to offer. We published the results in the *Archives*, in 1988. The design was very conservative and very strict. Reading our results, most people were surprised that clozapine was able to show superiority in this population. But it did, and those results led to the FDA approving clozapine for marketing, in 1990. That certainly is a study I'm extremely proud of. It's one of the most frequently cited papers in psychiatry over the past decade and I think it played an important role in setting the stage for a new generation of drugs. Clozapine did serve as a prototype for a new generation of drugs to be developed. Our findings suggested it was possible to have an antipsychotic medication that caused relatively few parkinsonian side effects and was superior to other drugs in certain types of patients. The findings were attributed to clozapine's novel receptor binding profile. It also had an important heuristic impact on the field, by suggesting we might be able to develop other compounds that could mimic clozapine's novel properties.

TB: What about the use of clozapine in other patient populations?

JK: Since the time of our first study, we have done other NIMH supported studies in which we compared clozapine with haloperidol in less severely ill patients who live in the community and our findings will be coming out in the *Archives* sometime next year. In this population, we also demonstrated the superiority of clozapine over haloperidol for positive, but not for negative symptoms. We are finishing a double-blind comparison of clozapine and risperidone in patients who live in the community; we already know that fewer patients are dropped for lack of efficacy in the clozapine group in comparison to the risperidone group. Interestingly, some of the risperidone patients do well and if we look at those patients who survive in the study, in terms of psychopathology, the risperidone patients although there are fewer, are doing just as well as the clozapine patients. At this point, it remains an open question whether the new generation drugs

can show advantages in treatment refractory patients. My read of the literature, as of December 1999, would be that clozapine would still have to be ranked as the number one drug, in terms of effectiveness in treatment refractory patients. It may be that drugs like risperidone and olanzapine also have some advantages over conventional drugs, such as chlorpromazine or haloperidol, but not quite to the same degree we see with clozapine. So, we continue to do studies with clozapine, trying to delineate the areas in which it is most effective. We also did studies using clozapine to treat patients with severe TD or tardive dystonia and found that clozapine was not only helpful in preventing TD, because of its' low risk of extrapyramidal side effects, but also in ameliorating abnormal involuntary movements in those very severe cases in which they persist after discontinuation of antipsychotic drugs. For some time, clozapine was the standard treatment of patients with Parkinson's disease that develop L-DOPA induced psychosis. Now, some of the other new drugs are beginning to play a role in that area. I should point out that clozapine is probably still underutilized. Many clinicians don't take advantage of the opportunity to switch to clozapine when other neuroleptics, like olanzapine and risperidone do not help.

TB: We have been talking about clozapine for some time, but I don't think you have mentioned the dose you have been using.

JK: In the original multi-center clozapine study we published in 1988, the dose of clozapine averaged about 600 milligrams a day. Now, we usually shoot for a dose of about 500 milligrams per day. European investigators tend to use lower doses, and that still remains an area of controversy. My read of the literature, and this includes data from the clinical studies as well as studies which employed blood levels of clozapine, is we probably want to shoot for a dose of 450 to 500 milligrams a day to make sure we have an adequate trial. But, if a patient doesn't respond, we should do a blood level and, if the blood level is low, we should try even higher doses because once someone has got to the point of needing clozapine, we should make sure they have an adequate trial.

TB: Did you try to correlate blood levels and receptor binding?

JK: We do blood levels if a patient hasn't responded to clozapine. We don't do them on a routine basis. The studies that have been done have correlated blood levels with clinical response. They have not always been correlated with measures of receptor binding in the central nervous system. But the results support the fact that clozapine does have some unusual characteristics.

TB: At the beginning, your interest was on the effect of clozapine in chronic patients, refractory to other drugs. But, didn't your interest shift to studying the effect of these drugs in acute patients?

JK: We are now comparing two of the new generation drugs, risperidone and olanzapine, in first episode patients. Most of the studies were conducted to obtain new drug approval from the Food and Drug Administration in relatively chronic patients who've had multiple episodes. If you look at the literature, on average, patients are in their late thirties and they've had more than five or six previous hospitalizations with a mean length of illness of over fifteen years. If we believe that these new antipsychotic drugs have novel properties, it's going to be very important to assess their impact at the onset of the disease and, subsequently, in patients who've not been treated with other antipsychotic drugs, so we can see the true impact of these drugs in terms of the evolution of negative symptoms, cognitive dysfunction, or even, brain morphology. The current study is an attempt to look at these issues longitudinally, and to begin to collect data for answering these questions. We also need data as to whether there are meaningful differences between the new antipsychotic drugs. They all seem to be effective. They all seem to have less extrapyramidal side effects in comparison to drugs like haloperidol. Whether they prove to be significantly better in terms of the course of the illness, compliance with treatment, and in relapse prevention remains to be seen.

TB: Any other area of research you would like to address?

JK: In the Hillside First Episode Studies, it appeared that patients, who had delay in treatment during their first episode, seemed to have a poorer response subsequently. Similar findings were reported by Eve Johnstone and by Phil May, as early as the 1960's. This has led to a tremendous interest in reducing the time between onset of illness and initial treatment. It has also become clear there are prodromal signs and symptoms in many cases of schizophrenia, including symptoms like depression, social withdrawal, suspiciousness, sleep disturbances, irritability, bizarre behavior, and ideas of reference. None of these symptoms would allow full diagnosis of schizophrenia, but when patients and families are interviewed, it's clear in many cases, there are early signs before the onset of full blown psychosis. The question now becomes, can we, with certainty, identify people in the prodrome and institute effective treatment that might reduce the risk of a full blown psychosis? Hillside has now established a clinic, which focuses on this area of research.

TB: So, there are certain manifestations that might be predictive for developing psychosis?

JK: Identifying these prodromal signs and symptoms does have some predictive value. If you combine that with family history, you're increasing the predictive power to justify routine treatment. We're beginning, in some cases, to use antipsychotic medication if we are seeing early psychotic signs and symptoms. We are also trying to identify social and environmental factors that play a role in delay of getting treatment. We have to do a much better job of training primary care physicians, other health professionals, and even general psychiatrists in rapidly and reliably identifying the early signs of schizophrenia, making sure patients get into an appropriate treatment setting to manage that phase of the illness. The public also suffers from the fear and stigma associated with mental illness, so even when a family is concerned about a young person demonstrating some worrisome or bizarre behavior, they may consciously or unconsciously deny that, because they're fearful of the consequences. We need a tremendous amount of public education outreach to physicians, clergy, and school teachers to narrow this gap.

TB: Any other area of research you have been involved with?

JK: There are a number of other areas. We've been involved in a number of clinical trials, developing new compounds. Another area is the issue of involuntary commitment. We published a paper a number of years ago, on what happen to patients' attitudes after involuntary commitment to hospital. We found that once patients responded to treatment, their attitudes towards involuntary hospitalization changed. In response to a series of questions, most patients said if this ever happened again, they would want you to do the same thing, which is very important, because when we discuss the issues of protecting their civil liberties and protecting them from harm, it can be a very difficult balance. There are patients providing proxy consent, so if they do become psychotic, they're giving permission to be hospitalized. That study was very helpful, in clarifying that patients were capable of understanding and appreciating the need for hospitalization. The other striking finding was that the overwhelming majority of patients, despite having been committed to the hospital on an involuntary basis, once they're out of hospital, did come back for treatment on a voluntary basis over a long period of time, which suggests that they recognized and accepted the need for treatment. Another area that we've been interested in and concerned about is the placebo response in schizophrenia. There's a lot of debate as to whether there should be placebo-controlled trials in any condition for which there's an effective treatment available, or should we just do active comparisons. I think there are very legitimate points to be made on both sides, but one of

the realities in schizophrenia research, involving affective disorders, is that response to treatment of proven effective antipsychotic medication is very heterogeneous and very unpredictable. We recently conducted a meta-analysis, involving hundreds of patients participating in controlled clinical trials, comparing proven effective antipsychotics and placebo for some of the new generation drugs, and what we showed was there was an enormous variability in the placebo response during the course of a four to six week trial. We also have historical data that shows an enormous variability in response to haloperidol during a similar four to six week period. All in all, it can be difficult to draw conclusions without a placebo group. On the other hand, there's legitimate concern about participation in a placebo controlled study when effective active treatments are available. I think it requires a consensus among patients, families, investigators, and governmental agencies, as to what's necessary scientifically and ethically appropriate. That debate is still going on.

TB: Could you tell us something about the different assessment instruments you are using in your research?

JK: There have been a number of scales developed over the years to measure different aspects of psychopathology. There's also a group, including Nina Schooler, who we recruited to Hillside a couple of years ago, working on a new scale which will hopefully be an improvement over previous scales in measuring both positive and negative symptoms. Rating scales have played an important role in helping to define clinical response, but they have been somewhat disappointing in capturing the array of domains in which patients with schizophrenia are affected. The field is still struggling with trying to develop a comprehensive set of instruments that would include both positive and negative symptoms, as well as cognitive functioning, psychosocial symptoms, and other factors relating to long term functional outcome. We've primarily utilized the BPRS. Peg Werner and others developed the BPRS Hillside version. We have a whole research unit focusing on that area. We're pleased with some of the results we see in the changes in psychopathology in short and long term clinical trials, but the real question is whether the patient can function in the community in a relatively normal way.

TB: What would you consider as your most important contribution to the field?

JK: Probably my work with clozapine, in demonstrating how important clinical research can be in developing newer and better treatments, and also, in playing a heuristic role for research on a

pre-clinical level. We'd like very much to be at a point where the etiology and pathophysiology of the disease are driving the development of treatment, but we're not there, as yet, in schizophrenia. So, we rely on clinical research and observations to establish advances in treatment and try to reason backwards from there to try to understand what implications this might have for mechanisms of action, pathophysiology, and so forth. Unfortunately, very high quality clinical research is not given the recognition and support it needs. I hope one of my major contributions, through the clozapine or prospective studies of TD, or the first episode studies, would be to demonstrate how valuable well designed, carefully conducted clinical research can be in setting the stage for further advances in knowledge, whether clinical or pre-clinical. TB: Is there anything specifically you would like to see to happen in your field of research? JK: We have not succeeded in understanding the mechanism of action of clozapine and there's a tendency to focus rather narrowly, on a number of different neurotransmitter systems involved. By doing that, we often arrive at premature closure. Also, it may very well be that schizophrenia is a number of different diseases and we still have a long way to go to understand the sub-types and different domains affected. It may be very naive to think one drug is going to simultaneously improve positive and negative symptoms, cognitive dysfunction, social withdrawal, apathy, and lack of motivation; that all of these will be alleviated by a single drug. It may be we need multiple treatments and not just pharmacologic ones, but also psychosocial treatments to be able to address all the domains of dysfunction we see in this disease we call schizophrenia. That's another area we hope we've made some contribution.

TB: So, you would like to see a more comprehensive approach to treatment?

JK: Right. We've recently recruited Anil Malhotra, who is focusing on genetic strategies to delineate sub-types and better understand pharmacologic response. The enormous excitement surrounding mapping of the human genome and explosion of knowledge that will take place in the genetic underpinnings of disease and pharmacologic response, is going to be one of the most exciting areas over the next decade.

TB: At the beginning of this interview, you talked about Don Klein, and later on you mentioned Jeff Lieberman. It seems Hillside provided a stimulating environment for research.

JK: Certainly, Hillside provided a stimulating environment for research. I talked about the role of Don Klein and other colleagues and that, in the early 1980s, I recruited Jeff Lieberman. I was

able to sponsor a research scientist development award for him in the mid 1980's, which enabled him to begin the new generation Hillside First Episode Studies. And Jeff continued that work for more than a decade at Hillside.

TB: Didn't Jeff work with you on methylphenidate? Could you elaborate on that?

JK: One of the issues has always been, can we do a better job of predicting drug response or vulnerability to relapse? There was still considerable debate about whether maintenance treatment should be on a continuing or intermittent basis for some patients. We thought, if there was some way to predict who might be vulnerable to relapse, we would know whether to make a concerted effort to keep a patient on medication. There were observations that dopamine agonists, given orally or intravenously, were capable of producing a transient exacerbation in psychotic signs and symptoms, and this was a methodology for identifying those vulnerable to relapse. I think the whole area of challenge studies has come under question as to whether or not that is something we should be doing, but these studies were done at a time when it seemed an opportunity to help, by establishing a better profile of what the risks and benefits of treatment would be. It was also applied in the first episode study as an attempt to understand the sub-types of patients, who might respond better or worse to treatment.

TB: You found clozapine superior to some of the other neuroleptics, and especially, to haloperidol. Did anyone replicate your findings?

JK: There have been a number of controlled trials with clozapine, conducted by Alan Brier, Sanjiv Kumra, David Pickar, and very large scale studies, conducted by Bob Rosenheck and Susan Essock, but the results are not always the same. Some studies have demonstrated clear superiority in measures of psychopathology, whereas other studies have shown superiority in rates of relapse or rehospitalization. But the superiority of clozapine has held up well across a number of studies. The irony is that there's not as many double-blind control trials on clozapine as there should be and a lot of the claims that have been made for clozapine have come from open and uncontrolled trials, so there's still a lot that needs to be done.

TB: Let me switch to some of your publications. You started to publish in the late 1970s, didn't you?

JK: There were a couple of papers that came out around the same time about the prophylaxis of unipolar and bipolar depression; it was one of my first major publications in the *Archives*. Data

from our first episode maintenance treatment study was an early report. Our work on the prevalence of tardive dyskinesia was also an early report.

TB: Were these papers published in the late 1970s?

JK: Late 1970s and early 1980s.

TB: What was your last publication?

JK: The last publication is one that's in press, which will be a report on, "The Six Month Comparison of Clozapine and Haloperidol in Moderately Ill Outpatients." That's the last paper in press, right now.

TB: Approximately how many papers did you publish?

JK: About two hundred papers and a few books.

TB: Were any of the papers or books translated from English into other languages?

JK: I think some of the papers have been, and the 1988 clozapine paper has something like seventeen hundred citations, so it's a citation classic, which I'm very proud of.

TB: You are the recipient of many awards. Didn't you recently receive the Heinz Lehmann Research Award?

JK: I was very pleased to receive that. Heinz Lehman was one of the pioneers in our field and it was a great pleasure to receive something with his name on it, particularly since I'd had the pleasure of knowing him. He was at the award ceremony. I've been very gratified to win a number of awards, including the Lieber Prize and the American Psychiatric Association Research Prize. I never expected any of those things when I went into research. It was purely a fascination with the challenge of trying to improve the treatment and it's always been a privilege to work in this field and be recognized for contributions.

TB: Is there anything we left out and should be on the record?

JK: The other thing I'm most proud of is that, for the past twelve years, I've been chairing the Department of Psychiatry at Hillside Hospital, one of the largest psychiatric hospitals in the country and that has a very strong research and clinical training tradition. I'm very proud of the fact we've been able to integrate research into a private, not for profit, psychiatric hospital, and to train a terrific group of clinicians and investigators as well as maintain a resource for people in the community and nationally in need of treatment. Probably the most gratifying is the acknowledgment and gratitude from patients and families helped by our work.

TB: So you have been active as a clinician, teacher, researcher, and administrator?

JK: Unfortunately, a few years ago, I made the decision to curtail my clinical practice, and so I'm seeing a very small number of patients now. But, as a clinical administrator, I'm involved in trying to provide state of the art care to thousands of patients, so I feel much rewarded by that.

TB: I think we should conclude this interview on that note. Thank you very much.

JK: Thank you very much.

37. MARTIN M. KATZ

TB: This will be a special interview with Dr. Martin Katz³⁹ for the International Archives of Neuropsychopharmacology of the American College of Neuropsychopharmacology, about the birth of the College and about the role of the National Institute of Mental Health (NIMH) in the founding of the ACNP. We are at the Boca Raton Resort Hotel in Boca Raton. It is December 12, 2007. I am Thomas Ban. So Marty, could you tell us about some of the background to the founding of ACNP.

MK: Thank you, Tom. Tom and I go back many years and lately we reminisce at annual meetings of the College, about how ACNP started. I am happy to be able to talk about some of the events that led to the founding of the college.

TB: Could you tell us briefly first how you got involved in psychopharmacology?

MK: As a young psychologist, I was doing research on the evaluation of psychotherapy and in other clinical areas in psychology and psychiatry. It was a very exciting opportunity for me, in 1957, to come to work at the National Institutes of Health (NIH) to help to begin the Psychopharmacology Program. It was made possible for me by Jonathan Cole, who at the time was the newly appointed head of that program.

TB: Could you say something about how this program came about?

MK: The establishment of a Psychopharmacology Program at NIH was the outcome of testimonies at the Congress from many psychiatric experts and lay professionals about the importance of the discoveries of some new psychotropic drugs in the mid-1950s. Introduction of these new drugs was by any stretch of the imagination a revolution in psychiatric treatment. These testimonials played a role in convincing the Congress of the United States of the need for a great deal of support from the Federal Government, to fund and to engineer the founding of a new discipline, neuropsychopharmacology, that could have a very great effect on the treatment of mental disorders

³⁹ Martin M. Katz was born in New York City, New York, in 1927. He received his Ph.D. in psychology from the University of Texas. After completing post-doctoral studies at the University of Texas, he went to Washington to work in the Veterans Administration Neuropsychiatric Laboratory. He was recruited, in 1957, as the Executive Secretary of the Psychopharmacology Service Center of the National Institute on Mental Health, and subsequently, progressed to become Chief of the Clinical Research Branch of NIMH. Upon his departure from NIMH, he was on the faculty of the Albert Einstein College of Medicine in New York City, and then, the University of Texas Health Science Center at San Antonio. He was interviewed in Boca Raton, Florida on December 12, 2007.

in this country and in the world. One of the people who testified before the Congress was Nathan Kline, a young psychiatrist at the time.

TB: Could you tell us something about Nate Kline?

MK: Kline played a role in introducing reserpine, one of the first “tranquilizers,” that was used in those days in treatment. He had a flamboyant presence, a very convincing manner, and was very adept at influencing US Congressmen and other people. He deserves a lot of credit for getting that first two million dollars from Congress dedicated to the NIH to begin this new program in Psychopharmacology. At the National Institutes of Health, there was another formidable figure; and that was Seymour Kety. He was in charge of the intramural laboratory program there. And, Nathan Kline and Seymour Kety were two of the members of the first National Advisory Committee on Psychopharmacology for the NIH. Their job was to make recommendations on how to spend two million dollars, which at the time was a very large amount of money, to initiate research in this new discipline, and to carry out certain projects and especially a very large collaborative controlled study, involving a large, representative sample of patients, on the effects of phenothiazine tranquilizers on schizophrenia. Most of the work done, up to that point, with these drugs had been done in smaller, “open” studies, which were neither controlled or “double-blind.”

TB: Who else were on the Advisory Committee?

MK: Others on this advisory committee were figures like Heinz Lehmann, the psychiatrist who introduced chlorpromazine, the first phenothiazine tranquilizer in the treatment of schizophrenia, in North America. Drs. Kline and Lehmann represented psychiatry on this committee. The Committee had to also include representatives of all the other disciplines, which were to make up this new field. That meant bringing together experts from the psychological, biological, and psychiatric elements of the field. So, we had scientists like Lou Goodman, who had written the principal pharmacology textbook in the medical field, and Louis Lasagna, a very creative pharmacologist, who was at that time at the University of Rochester, in New York. And, then, we had Howard Hunt and later, Gardner Lindsey, who were leading figures in the psychological field. We also had experts in the fields of statistics and epidemiology. The most formidable in the latter group was, I thought, Sam Greenhouse, who brought expertise in both statistics and in the clinical trials field. He was particularly critical in the development of the collaborative

program, as were Mort Kramer, who ran a major epidemiologic facet of the NIMH, and some other figures.

TB: Who was the chairman of the Committee?

MK: The Chairman of the Advisory Committee was Ralph Gerard, a world-renowned neurophysiologist. You can imagine the difficulties that they had in weaving psychology, psychiatry, and pharmacology together to create this new discipline. And, I, a young investigator, was given the task as the first Executive Secretary of this group, to observe and record the major points of their discussion, and the nature of activities that were going on in the new field. My eyes, of course, were very big at that time. The people on the Committee were very impressive. And the battles that went on in the committee were provocative and highly productive. It would be worth documenting them in more detail. Just to give you an impression, Nathan Kline, credited with influencing the Congress to appropriate the funds to get this field started, as I mentioned, was a rather expansive representative of the field, and he was not very well liked by Seymour Kety, a basic scientist. Kety thought that Nathan Kline had exaggerated, overestimated what the new drugs could do, and oversold the field to Congress. He wasn't too happy with the outcome and Congress' action. Everyone realized that if you did not present the case for expanding research on the new drugs in a salesman-like persuasive manner that the two million dollars would never have come in the direction of the Institute. So, those of us working in the program at that time, were not unhappy and weren't too critical of Dr. Kline. But, Dr. Kety had very sturdy principles in this respect and he and Dr. Kline were continuously arguing about the ethics and the direction the new program should take. I once labeled this the Battle of Saint Seymour and Nathan Kline, or something to that effect. Dr. Kety wanted most of this money to go towards basic research to provide the foundation in chemistry, pharmacology, and biology for the new field, whereas Dr Kline and Dr. Lehmann were for using a major part of the funds to carry out a very elaborate collaborative study, which would involve nine hospitals across the country, with many clinicians and many patients to demonstrate the effectiveness of the new drugs. Their idea was that if the sample is large and representative enough, then the results of the study could be generalized to schizophrenic patients at large across this country and other countries, and consequently the demonstration of the effectiveness of the new drugs would move the field ahead. So, the Battle was basic science versus

clinical science. But, the mission was clear in the Congress' recommendation, and we had a charge to carry out a collaborative study.

TB: How did Jonathan Cole get into the picture?

MK: Jonathan Cole, an extremely innovative psychiatrist and leader of the NIH psychopharmacology program, brought the research plan for the study to the Committee, and the Committee approved the funds to do the research he proposed.

TB: It seems that the Advisory Committee had a major role in starting the new field. MK: The Advisory Committee, consisting of ten to twelve members, established the structure for the field of Psychopharmacology. Soon after this cross-national clinical studies program at NIH got started, in 1960, the investigators began to act on the need for a national association, a scientific college.

TB: Could you elaborate on this?

MK: Because there were so many disciplines involved, it was a problem how to get the different disciplines to communicate with each other in order to solve the scientific problems unique to this new science. It required that researchers involved cross biological, psychological, psychiatric considerations in their research. It was in the course of this process, that the concept of the American College of Neuropsychopharmacology evolved.

TB: Could you name some of the people involved in the creation of ACNP?

MK: The early creators of the college were people like Paul Hoch, Jonathan Cole, Joel Elkes, Ted Rothman, and Dick Wittenborn. Elkes was a leading figure in the field; he had created the first Department of Experimental Psychiatry in the world in Birmingham, in the United Kingdom, by setting up a model for merging science and psychiatry. He was also one of the most eloquent spokesmen in the field, emphasizing the importance of linking basic and clinical research into the future. He had a major influence on my work as a young investigator because of his emphasis on the importance of creating a new clinical methodology in order to move the science forward.

TB: When was the College actually founded?

MK: In 1961.

TB: Were the annual meetings at the center of the activities of the new College?

MK: Yes. The first secretary/treasurer of the group was Ted Rothman. Then, it selected Dick Wittenborn, a scholar in psychology from Rutgers University with a long history of developing psychiatric rating instruments. He also had a flare for doing things well, when it came to organizing

conferences. Wittenborn established the home base for the annual meetings in Puerto Rico and set the annual meeting dates for the beginning of December. This location and date became a tradition that was maintained up to a few years ago. When the group was small, it worked beautifully well. We would meet for a week. There would be some formal presentations, but half, or full day “Study Groups” were the main features of the meetings. They covered a range of topics from the Neurochemistry of Mental Disorders to Transcultural Psychopharmacology. The idea was that we had to move the field of clinical science forward as we couldn’t wait for things to simply move on at their own rhythm, as they apparently do move in the basic sciences. The study groups were heavily invested in attacking problems. We also had a wonderful study group on “Drugs in the Year Two Thousand” that was later published as an ACNP volume. We tried to look ahead into the future; what would the field of psychopharmacology look like in the year two thousand from the knowledgebase of in 1970? If you are Westerners, and not from the Far East, where cultural representatives plan in ten and twenty year cycles, you are not likely to be looking more than a few years ahead. Most of us felt personally that we would not see the year two thousand. In that particular study group, we had celebrated people, like the novelist, Arthur Koestler, as one of the panelists, along with the anthropologist, Ashley Montague, and clinical scientists. And, when we look at the College’s 2008 annual meeting program, we now see a different picture, a very different set of topics, and a contrasting approach.

TB: So, you think that the meetings have changed and we have lost something with the change?

MK: I would like to see some of the spirit of the “study group” orientation from the early years in today’s program. It helped distinguish the College from other scientific associations. We might have lost that, because the College has become big and the emphasis has shifted from the clinical to the basic science world. However, some of the clinical issues have remained unresolved. I would say that many of the problems of how we bring together disciplines like neurochemistry, behavior, and pharmacology have remained unresolved and bedevil efforts to solve major problems like, for example, the “neurobehavioral” mechanisms underlying the effectiveness of the antidepressant drugs. I can, if I were to speak from a scientific basis, say that we still have not created those components that cross biological and behavioral spheres, a process that is necessary in order to understand how the drugs work. I don’t think we should be leaving that area of research as quickly as we appear to be doing.

TB: So, you think we should continue with the old type of study groups?

MK: Yes. It would be useful to invite outsiders, leading figures from other fields, to help extend our perspectives. We should also have plenary symposia that we had for example, in 1973, in which I was proud to have David McClelland, the chair of psychology at Harvard, Eric Strömngren, from Denmark, one of the leading world psychiatrists on the epidemiology of schizophrenia, Sol Snyder, one of the then rising investigators in the field of biochemistry and pharmacology, and the Nobel Laureate Linus Pauling. They stirred up our membership, especially Pauling with his ideas about the rigidity of scientific thinking, as he put it, the resistance to, and the subsequent unnecessary delay, in the acceptance of new scientific evidence. I think those kinds of symposia could be put together again, to maintain the uniqueness of the organization, and to stir us up again, to get us moving in the right direction.

TB: On this note, we should conclude this interview with Marty Katz. Thank you for sharing with us this information, Marty.

MK: And, thank you, Tom. Thanks for having me.

38. SEYMOUR KAUFMAN

TB: This will be an interview with Dr. Seymour Kaufman⁴⁰ for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the college in San Juan, Puerto Rico. It is December 11, 2002. I am Thomas Ban. Let us start from the very beginning.

SK: I was born in Brooklyn, New York, in 1924, and during the early part of my life, I was sure I was going to be an artist. I had talent, enough, so I got into a noteworthy high school in New York City called the High School of Music and Art, with a competitive entrance exam. It was during high school days, I became exposed to science and faced a conflict. I was very interested in chemistry. Being at the music and art high school, I was exposed to kids with real talent, and quickly realized I would never earn a living as an artist. So I decided to switch to science. That was a very wise decision, because my wife and I have a daughter who is a professional sculptress; she is really very good but is having a terrible time supporting herself. I started my advanced education at Brooklyn College and stayed for two years, and then decided that living at home I was missing something I expected college to do. So I made one of the very important decisions in my life. I decided to leave Brooklyn College and transfer to the University of Illinois at Champaign-Urbana. I selected Illinois because it had a reputation for an excellent chemistry department, and that is what I was interested in. I stayed there for my bachelors training and then got a master's degree. I would have stayed for my Ph.D. but they had a very sensible rule; they did not allow anyone to stay for all their degrees in one place. At that point, Dr. Hans Neurath, at Duke University in Durham, wrote to the chemistry department and asked if they had any graduate students who were strong in chemistry. He needed a chemist for his research program. So they recommended me and I went there to work on my Ph.D. That proved to be a good choice for several reasons. Neurath was an excellent teacher, so I learned a lot about protein chemistry and kinetics. Not only that, but I met my future wife who was getting her Ph.D. at the same time. In retrospect, I'm firmly convinced that one of the important factors in success in research is the kind of training one has, and I got excellent training with Hans Neurath. After that, I did a post-doc

⁴⁰ Seymour Kaufman was born in Brooklyn, New York, in 1924. He received his Ph.D. at Duke University in Durham, North Carolina. After post-doctoral studies at New York University, he took a faculty position at NYU Medical School. Subsequently, he was recruited to the Intramural Research Program of the National Institute of Mental Health where he remained throughout the rest of his career. Kaufman died in 2010. He was interviewed in San Juan, Puerto Rico on December 11, 2002.

with Severo Ochoa, at New York University, before he won his Nobel Prize. I was there only one year, when he offered me a position on the staff at NYU medical school. I ultimately stayed for five years. With Severo, I learned a lot about enzymology that complemented what I had learned with Hans Neurath. After five years, I was offered a job at the National Institute of Mental Health in Giulio Cantoni's department. I think it was called General and Cellular Pharmacology. I had got to know Cantoni while he was a postdoc with Dr. Ochoa, during the time I was there. Around this time, Cantoni moved to NIMH to start a new laboratory, and Giulio offered me a position to join him. I went to the National Institute of Health, in 1954, and I am still there. In 1970, I was offered an independent laboratory of neurochemistry at NIMH. NIH proved to be a very fine place to do research in those days.

TB: Could you say something about your different activities before you went to NIMH?

SK: During the time I was with Severo Ochoa, his great interest was enzymes in the citric acid cycle involved in the metabolism of carbohydrates.

TB: Was that your first research project?

SK: No, I had done a master's thesis at Illinois that dealt with fatty acid oxidation in leukemia. There was an observation that leukemic mice had fatty livers, and my thesis advisor, Dr Carl Vestling, said if they have fatty livers maybe they have a defect in fatty acid oxidation. My goal was to either prove or disprove that thesis. And we found a significant defect in fatty acid oxidation.

TB: This was your master's thesis. Was it published?

SK: It was my first publication in *The Journal of Biological Chemistry*. Unfortunately, in those days, not much was known about fatty acid oxidation, so we couldn't continue the analysis to pinpoint what was wrong. But it was a very good introduction to research and culminated in a publication. At Duke, Neurath's great interest was proteolytic enzymes; we had three graduate students, and each was assigned one of the proteolytic enzymes to work on. The enzyme I was assigned to was contripsin and my wife's was capoxy peptidase. The enzyme I was on was known to require an aromatic amino acid. So I prepared amino acid ethyl estrins to test them as inhibitors because they were supposedly good candidates for being inhibitors. To my great surprise, we found that they were excellent substrates for the proteases. Each one of us, in turn, demonstrated the same phenomenon with respect to proteases. In those days, enzymes were thought to be much

more specific than they are now, so, this was quite a startling finding. In retrospect, it doesn't seem astonishing, but it was at that time. It's fair to say it gave Neurath's career a push. It gave my career a big push, too. Then, I moved to NIH. At NIH, I had a bit of good luck. It started out as bad luck because the laboratories we were supposed to occupy were not finished. So for about six months, I didn't have any place to do research. I thought that was a tragedy but it turned out to be a blessing because I spent the time in a library thinking, a rare commodity, trying to decide what kind of project I would work on. I knew I wanted to work in some aspect of enzymology and decided I would select an enzyme reaction where you couldn't easily write the equation. I figured that if the reaction was so mysterious you couldn't write a simple equation, there might be something unknown, something interesting. The reaction I chose to study was the conversion of phenylalanine to tyrosine because if you write that down on paper, the only way to have a balanced equation is phenylalanine plus half an oxygen molecule.

That's fine, except there is no such thing as half an oxygen molecule in nature, so there was clearly something mysterious. In addition, I wanted a project that had some elements of a double acrostic puzzle. I don't know if you're familiar with them, but they come out in the *New York Times* periodically, wherein you solve the puzzle in one dimension and the first letter of words in the vertical dimension spell out the author's name, while in the horizontal dimension, the quotation is spelled out. If you solve the horizontal direction, the solution to the vertical problem comes automatically. It seemed to me that phenylalanine hydroxylase had some of the elements of a double acrostic puzzle, because I was aware of a genetic disease called phenylketonuria, and it was known that there was something wrong with phenylalanine metabolism in the patients. Not a whole lot more than that was known and I had a feeling that if I could advance our understanding of the way phenylalanine was hydroxylated, out of that might come some new information about phenylketonuria. So, that was a double reason for selecting the project. Using the methodology I learned in Ochoa's laboratory, specifically how to separate a complex system into its individual parts, I started to work on the phenylalanine hydroxylating system in rat liver, and very quickly, broke it down into different components, two enzymes and a nonprotein cofactor. You asked me to point out what I thought was my biggest accomplishment. Working on the structure of this nonprotein factor and proving its structure was certainly one of the biggest accomplishments in my life. It took me a couple of years to work out the structure and it turned out to be a compound

whose derivative was present as a natural component in human urine. No one had ever detected in liver the parent of that component in urine. So I isolated the natural cofactor from rat liver and proved that it is tetrahydrobiopterin. Biopterin is a pteridine and another compound in nature which is a pteridine is folic acid. There is a slight resemblance between biopterin and folic acid. But biopterin itself is not a vitamin, because we can synthesize it, whereas folic acid, being a vitamin, we cannot synthesize. So, we slowly tried to unravel what the role of the three components was, two enzymes and the cofactor. It turned out that the role of one of the enzymes, which we named dihydropteridine reductase, was to regenerate tetrahydrobiopterin, which during the course of hydroxylation gets oxidized to dihydrobiopterin. In order for it to work in the body, it has to function catalytically. The role of the second enzyme was to reduce the biopterin back to the tetrahydro level. Then we quickly realized there might be at least three different forms of phenylketonuria. One caused by a lack of each of the essential components. In fact, it was already suspected that the cause of phenylketonuria (PKU) at the enzyme level was a lack of phenylalanine hydroxylase. Jervis had shown that. But Jervis didn't know about the multi-component nature of the hydroxylating system. Jervis had pinned down which was the missing component. It could have been any one of the three components. I managed to get biopsy samples from two PKU patients and showed they had normal amounts of tetrahydrobiopterin and that the only missing component of the hydroxylating system was phenylalanine hydroxylase. The other two components were present in adequate amounts. Having done that, we realized there might be variant forms of PKU, caused by a lack of reductase and biopterin. So we were primed to expect to read about that. Not being a clinician, I didn't do the initial work on that. About ten years went by, and there were no reports of the expected variant forms, and then, I remember the day I received a call from a pediatrician, Tony Holzman, at Hopkins. I had met him at a scientific conference. He said they had a PKU patient who was a couple weeks old, who was on the accepted treatment for the disease; a low phenylalanine diet. In order to be effective, the diet had to be instituted very early in life, within the first couple of weeks. Holzman said the child had what pediatricians describe as a failure to thrive. He just didn't look right. And he wanted to know if he could supply us with a biopsy sample of the liver that we could analyze for the three components. He suspected that there was something funny about this particular child. So I said, send us a piece of liver, which he promptly did. In one afternoon we assayed for all three components and showed that

there was not a trace of the reductase in this child's liver. He had adequate amount of the cofactor and adequate amounts of hydroxylase. So this was the first established case of a variant form of PKU due to the lack of reductase. In contrast to classical PKU, which is caused by a lack of the hydroxylase, this variant cannot be treated with a low-phenylalanine diet. And the reason why is that we, and others, had shown that tetrahydrobiopterin and the reductase were essential components of tyrosine hydroxylase and tryptophan hydroxylase. Just withholding phenylalanine would cure only one part of the disease these children suffered from. They had three metabolic lesions, and you had to treat all three. We suggested in our first publication they had to be treated with the neurotransmitter compound beyond the block in their metabolism; with 5hydroxytryptophan for the block in tryptophane hydroxylase, and DOPA, for the block in norepinephrine synthesis, in addition to a low-phenylalanine diet. Unfortunately, this treatment was started too late and the child died. So, these variant forms of the disease used to be called malignant or lethal forms of PKU. Subsequently we were contacted about other children, who looked like good candidates for reductase deficiency. And they were adequately treated with neurotransmitter precursors. A couple of years after that publication, I was contacted by another pediatrician, Dr. Stan Burlow, from the University of Wisconsin, and he also had a child who was not doing well and wondered whether there was still a different variant of the disease. He sent us a liver biopsy from his patient, and we showed that the child was deficient in tetrahydrobiopterin, with adequate amounts of reductase and of hydroxylases. So, this was the second variant form of PKU that we have described, PKU caused by a lack of an enzyme involving tetrahydrobiopterin synthesis. These were very rewarding studies, the discovery of two new diseases and their treatment. I should say that treatment, for the lack of tetrahydrobiopterin, is not very satisfactory yet. You would think the natural way to treat them would be to just give them tetrahydrobiopterin, what they are missing. But tetrahydrobiopterin does not cross the blood brain barrier readily. Nonetheless, it is used. It will cross the barrier to some extent. But, the treatment is not ideal; a better treatment is required. What I regard as my most important findings were the isolation of tetrahydrobiopterin from the liver, and the discovery of the variants of phenylketonuria.

TB: What is the time frame of the research?

SK: From the time I first went to NIH, from 1954, until I retired about two years ago.

TB: It was one major continuous research effort?

SK: Yes. The other important contribution was when I found that tetrahydrobiopterin was the cofactor for phenylalanine hydroxylase; I had no idea how general a role tetrahydrobiopterin played. It was clear from its involvement with both tryptophan and tyrosine hydroxylase and phenylalanine hydroxylase that it was a cofactor for aromatic hydroxylations of various kinds, and I wondered whether it was also involved in what is called a side-chain hydroxylation. In the pathway for norepinephrine synthesis is an enzyme that catalyzes the conversion of dopamine to norepinephrine that involves the side chain hydroxylation of norepinephrine. So we were interested in whether tetrahydrobiopterin was a cofactor for that hydroxylation. We worked on the enzyme that ultimately went by the name of dopamine- β -hydroxylase. In fact, we showed that tetrahydrobiopterin was not the cofactor for that enzyme, but instead ascorbic acid is the cofactor. In the course of answering this question we discovered one of the few well demonstrated metabolic roles for vitamin C. Just as tetrahydrobiopterin is oxidized during the course of phenylalanine hydroxylation, ascorbic acid is oxidized during the conversion of dopamine to norepinephrine. That was the first insight as to how metabolically vitamin C can work in the body.

TB: When was this shown?

SK: In the mid 1960s. That work is not as appreciated as it should be. If you read a nutrition book about vitamin C, they often don't mention that this is one of its important roles in metabolism. It needs to be publicized more. This about summarizes my scientific career.

TB: These were major contributions.

SK: There is still a lot of room for improvement in the treatment of these variant diseases.

TB: You said that you retired two years ago. Does this mean that you stopped going to the Institute?

SK: I go in once or twice a week. I was granted emeritus status and still retain part of an office. I have access to secretarial help, but I no longer have any post-doctoral fellows.

TB: Are you involved in any research?

SK: Very indirectly. I get asked to review a lot of scientific papers, but I'm less interested in reviewing papers than I was when I did research.

TB: Are you on the editorial board of any journals?

SK: No. I feel I put in my time as an editor of The Journal of Biological Chemistry (JBC) and Archives of Biochemistry. I worked ten years for the JBC. I mentioned I started out early in life

thinking I would become an artist, and after retirement, I tried to pick up that interest, to take some art courses.

TB: What kind of courses are you taking?

SK: Hand-eye coordination is very important in art, so the first way to get back into art was to take a life-drawing class. My daughter agreed with me. And so, I took several life-drawing classes, drawing the nude figure. I took those at the Corcoran Museum School. Most recently, I took a course on etching at Montgomery College. Those were both very enjoyable. And I did write a book on tetrahydrobiopterin along the way.

TB: When was it published?

SK: In the mid '90s, by Johns Hopkins University Press.

TB: Was that the only book you wrote?

SK: Yes. I also edited several books of research.

TB: Can you mention just a few?

SK: I edited one volume in a series called Methods in Enzymology that was started by Sidney Colowick and Nathan Kaplan and published by Academic Press. They asked me to edit their book on aromatic amino acid methodology. And I was the editor of several different symposia dealing with amino acid metabolism. That's about it.

TB: Is there anything we left out that you would like to mention?

SK: I am thoroughly enjoying my retirement. It's very important to have structure to your life. Some of my retired friends seem to be at a loss as to how to spend their time. But if you plan ahead, I think it can be a very enjoyable part of life.

TB: You seem to be quite a sportsman.

SK: I was. Now I'm less so.

TB: What were your sports?

SK: Mainly tennis. One of the bad effects my heart surgery had, for some reason, it interfered with my ability to walk. I had a lot of physical rehabilitation and it has improved a good deal, but not enough to play tennis. I do miss that.

TB: When did you become a member of ACNP?

SK: Maybe 15 years ago.

TB: Have you participated in the activities of the College?

SK: I regret to say I have not.

TB: Did you attend the annual meetings?

SK: Yes, I attend the meetings religiously.

TB: Did you present at the annual meetings?

SK: I was invited several times. I presented a few years ago at the symposium on tyrosine hydroxylases. Steve Paul organized it and I gave a lecture.

TB: You talked about your mentors at the universities.

SK: Hans Neurath and Severo Ochoa.

TB: Can you say something more about Neurath?

SK: Neurath was very demanding of his students. He transmitted that attitude to me, and I tried to transmit it to my post-docs. But he was a man of great integrity. He never cut any corners when it came to doing the ethical thing. Both my wife and I were very fond of Hans.

TB: During your career you trained many people. Would you like to mention a few? SK: Most of them went into enzymology. One of my best post-docs was Daniel Fisher. He was one of my earliest ones. Unfortunately, he left biochemistry and went into psychiatry. Michael Davis did important work in my lab. Unfortunately, he left and became a lawyer. And then there is a young fellow by the name of Bruce Citron. He was important in the evolution of my laboratory because he was well trained as a molecular biologist. It was very hard to find someone willing to be the only molecular biologist in an environment of enzymologists. Bruce was daring enough to do it and he spent five years with us. He helped us a lot.

TB: What was your last publication?

SK: It turned out that there was still another surprise about the phenylalanine hydroxylating system. I was working with purified enzymes of the system, assaying the phenylalanine hydroxylating reaction under conditions away from what we call ideal, slightly more alkaline conditions, and found there was a factor in liver that could stimulate the reaction. It came as a great surprise. We thought that we had identified all the components required for hydroxylation. Well, it turned out there was still one more component at least. We purified that component from the liver, using an assay based on the stimulation I observed. That discovery proved to take a very surprising turn, which ties in with the fact that our lab had got into molecular biology at that point. We purified that protein to homogeneity with no idea what it was doing. One of the first things we

wanted to know was whether or not it was a known protein. With the tools of molecular biology, you can do partial DNA sequencing, and see if there is any enzyme or protein already described that has a sequence in common. To our great surprise, there was a protein already described that had the same sequence as the protein we isolated. That protein went under the name of DCoH and had a well-established role in gene transcription in the liver. A man by the name of Crabtree, at Stanford University, had found that. So I called Dr. Crabtree, and said we've isolated a protein from liver that has the identical sequence to your DCoH protein, only our protein has a role in phenylalanine hydroxylation. He was as astounded as I was and agreed we would exchange proteins. I sent him a sample of our pure protein, he sent us his. His protein had as high an activity in the phenylalanine hydroxylating system as ours did in the gene transcription system, purified by a totally different procedure. We went on to prove that the protein had a role to play in hydroxylation and catalyzed the regeneration of tetrahydrobiopterin from the dihydro form. That was a step that normally would take place non-enzymatically, one wasn't aware of it, the reaction just occurred. But under the funny assay conditions I had accidentally set up, the non-enzymatic reaction was rate-limiting, and required the presence of this other enzyme to catalyze it. Immediately, we realized there was a possibility for still another variant form of PKU, one caused by the lack of this enzyme. We called it a dehydratase. We did manage to get a liver biopsy and show that there was a patient with a very rare form of PKU that lacked dehydratase. A few other centers in Europe made similar findings. The children that have been described, so far, are not really sick. They have hyperphenylalaninemia, but it is fairly mild, which is not surprising because this reaction also occurs non-enzymatically. Even if they lack the enzyme, they can survive pretty well without it. I'm looking forward to seeing the next phase of PKU research, which will probably deal with gene supplementation.

TB: Is this what you would like to see?

SK: I would say we are a couple of decades away from that.

TB: Is there anything else you would like to see happen? How do you see the future?

SK: There is an adequate dietary treatment for phenylketonuria, but it is a pretty awesome burden for the family and the patient. They can't eat any natural foods and subsist on an artificial mixture of amino acids, from which phenylalanine is removed. There is a lot of room for a better treatment. I can only imagine that gene therapy would be the wave of the future for the disease.

That's what I hope, will happen within the decade, but I'm not terribly optimistic.

TB: Anything else you would like to add?

SK: No, I think that's about it.

TB: On that note we conclude this interview with Dr. Seymour Kaufman. Thank you very much.

SK: I enjoyed it. Thank you.

39. JOSEPH KNOLL

TB: This will be an interview with Professor Joseph Knoll⁴¹ for the Archives of the American College of Neuropsychopharmacology. We are at the Department of Pharmacology and Pharmacotherapy of Semmelweis University, in Budapest. It is January 23, 2002. I am Thomas Ban. Let's start from the very beginning. Please tell us when and where you were born and say something about your early interests and education.

JK: I was born on the 30th of May 1925 in Kassa, a city in northern Hungary (now Kosice in Slovakia); but my parents moved to Budapest when I was three weeks old and where I have lived since. As a matter of fact, I had seen Kassa (Kosice) only about 40 years later. As a child, we lived in the outskirts of Budapest, called Kispest that translates into English, Little Budapest. As a teenager, I had to travel quite a distance by streetcar to high school that was located in the center of the city. In Hungary, we have eight years of high school, called gymnasium, after four years of grade school. I was lucky to get admitted to the Jewish Gymnasium that was an excellent school, where I learned a lot. From my very early childhood, I wanted to be a physician. I can't tell you why; there were no physician, before me, in our family.

TB: When did you graduate from high school?

JK: I graduated in 1943. It was a very difficult year. Hungary was an ally of Nazi Germany, and as a Jewish family, we suffered a lot that year. Although I was on the top of my class in the gymnasium, I was not admitted to medical school because I was Jewish. So, I had to take a job, instead of going to the university. Then, in March 1944, the German army occupied Hungary. Shortly after, my family, as all Jewish families, was moved into houses marked by the yellow Star of David.

TB: Did you have any siblings or was it just your Mother, Father, and yourself?

JK: I also had a brother, who was two years older than me. But, soon after the German occupation, he was called for service in the special division of the army for Jews, called "munkaszolgálat" that translates, literally, as "labor service." Before he left from home, we agreed that I would take care of our parents, if anything happens. We were prepared for the worse.

⁴¹ Joseph Knoll was born in Kassa, Hungary in 1925. After the Second World War, he attended the Medical University of Budapest where he received his M.D. and has been in the Department of Pharmacology throughout his career. He was interviewed in Budapest, Hungary on January 23, 2002.

TB: So, you stayed with your parents.

JK: Shortly after my brother left, I was also called for service, but in May, when I learned from the news that all the Jews from the suburb where my parents lived will be “deported,” and taken to a concentration camp; I deserted from the army and joined my parents in Kispest. I felt that they were too old to be left alone, and I wanted to be with them. So, I managed to be transported with my parents to Auschwitz. But we were not left together for long. As soon as we arrived to our destination, we were separated immediately; and they were sent to the gas chambers and killed. There is no way in conveying the feeling to anyone, who had not lived through that experience. I was left there alone. For days, I was in a daze; I was kept alive by the poems I knew by heart.

TB: You were kept alive by the poems you knew by heart?

JK: It was my Mother who introduced me to poetry. I like books, and by the time I finished high school, I knew by heart about 200 poems. And, I kept on reciting those poems I knew, and used to recite, as a child, to fall asleep. But this time, I kept on reciting them over and over again, for keeping me in contact with humanity, for not losing faith.

TB: When did you arrive in Auschwitz?

JK: I arrived in Auschwitz, in June, and was barely there for three weeks, when I was almost killed. Every day, a few of us had to carry the dinner, usually a dirty vegetable soup, in large wooden containers, from the kitchen to the outside, where the other inmates were waiting for the food. The chief of the kitchen, a huge two meters tall sadistic Lithuanian SS, was standing at the door of the kitchen, and while counting the containers, he struck with his stick the back of the man carrying the container, who just passed. He knew that those of us who were already weakened by starvation would fall or spill the soupy dirt from the container. And those of us who fell or spilled soup, he dragged to the kitchen, and beat them to death or until they lost consciousness. And this is what happened to me. And I would have died, if Joska Wegner had not saved my life.

TB: Who is Joska Wegner?

JK: He was another inmate from Kispest; a very strong man, a former boxing champion. He was, by that time, the leader of a group of inmates working in the Lager’s bread and food store for the drawing of rations. He found me unconscious in the kitchen, carried me to our barracks or “Lager,” as they used to call it, and arranged to have me in his group. We had to work hard in the store, but we could eat as much as we wanted.

TB: Did you work in his group all through the time you were in Auschwitz?

JK: No. One morning, the commanding officer was looking for an inmate, who spoke German. I spoke German with my Mother, at home, and Yiddish with my father, I was fluent in German; he picked me to become his servant. He treated me well; I think he really liked me. I remember that I always got a taste from the cookies and pastries his wife sent him.

TB: How long were you in Auschwitz?

JK: From June to September. When I was taken from Auschwitz to Berlin, I was in good physical condition; I weighed 78kg. Compared to some of the Polish prisoners, I was not in Auschwitz for very long. But, it was long enough to see the flames and the fumes of the gas chambers that worked all the time at full capacity, where thousands of Hungarian Jews and others, were killed and cremated.

TB: So, you were transported from Auschwitz to Berlin.

JK: To Berlin, first, and then, to Ohrdruf. I remember that in Ohrdruf, I was beaten up and left tied up for 24 hours in the freezing cold for stealing potatoes to curb my hunger. By the time I was untied, my hands and feet were frozen.

TB: Were you liberated in Ohrdruf?

JK: No, I was liberated in Dachau. From Ohrdruf, we were transported to Buchenwald. It happened here that when we arrived and were marching towards the Lager, I heard guns shooting and saw that people around me were falling to the ground. We did not stop and kept on moving towards the main gate of the Lager, but only a few of us made it. I think that everyone who turned back to see what was happening was shot, but I will never know what happened. From Buchenwald, I was immediately further transported to Dachau. It took 21 days to get from Buchenwald to Dachau, and only a few of us survived it. We were on the train that was to be called the "Dachau death-train," without being given any food or water. I was one of the few survivors and weighed 37 kg, when we arrived to Dachau. I was fully conscious but unable to move. The next day, after our arrival to Dachau on April 29, 1945, our "Lager" was liberated, by American soldiers. Most of them were black. Each of us was given a loaf of bread and a can of meat; thousands of us died, after taking the first food after being starved for weeks. It took me several weeks to get back my strength and learn to walk again. Since my English was fairly good, I became a clerk in Captain Schlenker's office, who was very helpful to me. He even offered me to get a

scholarship in the medical school of Zurich. I turned it down because I firmly hoped that my brother was alive and I wanted to return to Budapest to meet with him. Although Captain Schlenker warned me of the slim chance of my brother's survival, I still decided to return. Unfortunately, he was right, I also lost my brother.

TB: When did you arrive in Budapest?

JK: I arrived in Budapest, on September 8, 1945, and I soon learned that from my family, only an aunt of mine survived, and a niece, who was later to become my wife. I was left alone and had to start to rebuild my life. I wanted to enter medical school, immediately, but it was too late to register. So, I applied and was admitted to the Muegyetem, the Technical University, in Budapest, where they trained engineers. But after the first semester, in February 1946, I managed to transfer to medical school. So, in the summer of 1946, I was given the opportunity to take the courses and examinations of the first semester that I missed. I graduated from medical school, in 1951, with summa cum laude. I wanted to become a clinician, a neurologist or a psychiatrist, but I also thought that I should get some research experience before becoming a specialist. As a good student, I was one of the best in my class, I had no difficulty getting a job as a demonstrator in a basic science department, while still studying. I was very impressed with the famous scientist Geza Mansfeld, our professor of physiology, and my intention was to apply for a job in his department. But he got seriously ill and passed away. Then, in February 1949, I took my final examination in pharmacology and Professor Bela Issekutz, our professor of pharmacology, asked me whether I would like to work in his department. I was very happy to have this opportunity and joined the department. It was also important that the Hungarian Academy of Sciences was reorganized, just about the time that this happened, and I was able to get a stipend from the Academy to live on.

TB: So, you joined the Department of Pharmacology, in February 1949.

JK: And I have never left the department since. At the time the department was still on the second floor of the old building of the medical school. I fell in love with my work and have not become a clinician. But, I always kept in close contact with the clinical faculty of the university. I loved so much my work that I gave up, even chess, to be able to spend all my time in research.

TB: So, you were playing chess in your free time.

JK: I loved to play chess and was on the chess team of the Jewish Gymnasium and of the University, but I gave up playing chess because it distracted me from my work.

TB: What was your first project in the department?

JK: I was studying cholinesterase, the enzyme involved in the metabolism of acetylcholine. My research dealt with morphine and cholinesterase. I studied the synergism between morphine and prostigmine, a cholinesterase inhibitor. By the time I graduated from medical school, I had seven papers published on this topic.

TB: What was your next project?

JK: In about 1951, I started the project that I was to become engaged with for the rest of my life. It is concerned with the physiological basis of life, the brain, itself.

TB: How did you get involved in CNS pharmacology?

JK: I never worked in any other field. I entered pharmacology just about the time when the development of neuropsychopharmacology began and it became the center of my interest. I was a member of the team in Hungary that was involved studying chlorpromazine, imipramine, and desipramine; it was in the early 1960s that I developed deprenyl.

TB: Before moving to the 1960s, could you tell us something about your research in the 1950s?

JK: When I started to work in the 1950s, I had to find a method that would link CNS physiology and pharmacology. It was during the 1950s that I became interested in the “activating system” of the brain. And, when in the early 1960s, experimental tools specifically influencing the operation of the catecholaminergic and serotonergic systems in the brainstem were developed, I thought that they provided the key to the understanding of the operation of the brain. I became especially interested in what is responsible for what we call, drive.

TB: You used the term “activating system.” Were you referring to Moruzzi and Magoun’s “reticular activating system”?

JK: Let me give you a simple example what I mean when I refer to an “activating system” in the brain. A rabbit is eating cabbage in a relaxed manner and an eagle comes, and with lightning speed, tries to capture the rabbit. The rabbit, to survive, has a split second to change the activation process in the brain. In that split second, it must change from the relaxed situation to its maximum activity, to be able to use all its capacities to escape. I’m referring to the system that makes it possible for the rabbit to escape. There is a mechanism, I call “enhancer mechanism,” responsible for this activation, in which endogenous monoaminergic substances, such as noradrenaline, dopamine, and serotonin are released. And I have been interested in the regulation of “enhancer mechanisms” and

also in developing substances involved in “enhancer regulation.” From the different agents that have an effect on enhancer regulation, so far only β phenylethylamine (PEA) and tryptamine have been experimentally analyzed. I developed drugs for enhancer regulation. In the early 1960s, I had developed deprenyl, a synthetic, phenylethylamine derived enhancer, and in the late 1990s, I developed (-)-BPAP, essentially a tryptamine derived selective and highly potent enhancer substance.

TB: You mentioned that you did research with some of the newly introduced psychotropic drugs in the 1950s but did not say what you did.

JK: When chlorpromazine was introduced, in the mid-1950s, I developed two tests for the differentiation between classical sedative-hypnotic drugs and the new tranquilizers. One was based on a jumping reaction, and the other on hunger motility. We found, using these tests, that the new tranquilizers selectively blocked the conditioned reflex, whereas the old “hypnosedatives” blocked both unconditioned and conditioned reflexes. I presented my findings in a paper at the first CINP congress in Rome. Do you remember that congress?

TB: I know of that congress from my activities in the CINP’s history committee. It was held in 1958, about a year after the CINP was founded. Emilio Trabucchi, the professor of pharmacology in Milan, organized it.

JK: Daniel Bovet, one of the founders of the CINP, invited me to participate in that congress. It was my first trip to the West.

TB: So, you were invited to participate in that congress by Daniel Bovet, the Nobel Laureate?

JK: Yes, by Daniel Bovet. He was the President of the first CINP Congress. He got the Nobel Prize, in 1957. Bovet was interested in my research on the “active focus.” He recognized the importance of my research; later on, we became friends and collaborated in research projects; I used to send my assistants to spend some time in his laboratory, in Rome.

TB: So, Bovet was interested in your research in the “active focus.” When you say, “active focus,” could you tell us what you are referring to?

JK: I refer to a special form of excitation, in a particular group of neurons that provides the basis of an acquired drive. I developed, in the 1950s, a rat model to follow changes in the brain in the course of acquisition of a drive, from the start of training until it becomes manifest.

TB: Didn’t you write this up in your first book?

JK: Yes, I did, with the title *The Theory of Active Reflexes: An Analysis of Some Fundamental Mechanisms of Higher Nervous Activity*. It was published, in 1969, jointly by the Publishing House of the Hungarian Academy of Sciences, in Budapest, and the Hafner Publishing Company, in New York.

TB: Could you elaborate on your theory summarized in this monograph?

JK: According to my theory, the appearance of the mammalian brain, with its ability to acquire drives, ensured the development of social life and ultimately led to the evolution of the human society. This most sophisticated form of organized life on earth is still in the trial and error phase of its development. It seeks to outgrow the myths-directed era of its history, and arrive at its final state, a rationally organized human society. Furthermore, in the mammalian brain capable of acquiring drives, untrained cortical neurons (Group 1) possess the potential to change their functional state in response to practice, training, or experience in three consecutive stages, namely, by getting involved in (a) an extinguishable conditioned reflex (ECR) (Group 2); (b) in an inextinguishable conditioned reflex (ICR) (Group 3); or (c) in an acquired drive (Group 4). The activity of the cortical neurons, belonging to Group 3 and 4 is inseparable from conscious perception. In any moment of life, self is the sum of those cortical neurons that have already changed their functional significance and belong to Group 3 or 4. In the early period of my work, I wanted to show by EEG that there is a difference between an extinguishable and inextinguishable conditioned reflex, but our laboratory was poorly equipped, in the early 1950s. It's a very long story.

TB: Tell us the story.

JK: The story began with my interest in drives.

TB: What is your definition of a drive?

JK: In behavioral studies, "drive" is the force that activates the mammalian organism. There are innate drives of a limited number in the service of indispensable (vital) goals. The analysis of innate-drive-dependent functions (maintenance of homeostasis, fight for survival, feeding, sexuality, progeny-care, etc.) constitutes the main body of literature on behavioral physiology and endocrinology. Though innate drives are primarily based on sub-cortical regulations, none of the goals can be reached without the participation of the cortical neurons. Exclusively, innate drives keep the majority of the mammalian species alive.

TB: What about acquired drives?

JK: The capability to acquire an irrepressible urge for a goal, which is not necessary for survival of the individual or species, represents the most sophisticated function of the telencephalon. Though the development of an acquired drive always originates in one way or another in an innate drive, this relation becomes later unrecognizable. Humans are the only living beings on earth, whose life is predominantly based on acquired drives. To a certain extent, a minority of the mammalian species (the monkey, dog, horse, dolphin, rat, etc.) possesses this endowment, which, under natural conditions, remains unexploited. Nevertheless, humans obviously discovered thousands of years ago, probably through a kind of serendipity, that the behavior of such animals can be modified by proper training, and this started the development of the domestication of various species. The ambition to be in a permanent state of activity is a natural endowment of the human brain, which acquires drives with utmost ease. Look, in goal seeking behavior, this is the essence of life; the nature of the drive determines the goal and determines the fixation of the millions of chains of inextinguishable conditioned reflexes, the “knowledge,” needed to reach the goal. The mechanism is simple, always the same, but the drives and the goals determined by them, are immensely different. Thus, the essence of my theory is that an immortal poem is created by, essentially, the same mechanism as a pair of shoes. Since the basic mechanism operates also in animals capable to acquire drives, I studied it from the early 1950s, in the rat and summarized my findings and conclusions in my first monograph. The acquisition of proper drives in the most sensitive developmental period of life, from weaning until sexual maturity, will thereafter be determinant for the lifelong basic activity of the individual. It is obvious that since the fate of most individuals is still governed by the position in the society into which they are born, only a minority is lucky enough to acquire professional drives, in full harmony with natural endowments. The majority, as a matter of fact, forms - under coercion - the work-related drives that will ensure the place of the individual in the society.

Conformity between one's innate abilities and acquired work-related drives is of key importance for lifelong equilibrium. However, not only the desire to be permanently active is a natural endowment of the human brain, but there also is a need for a new challenge to one's drives in due time. Even the most satisfying professional drive becomes boring after its permanent, continuous use and there is a need to continue to keep the brain in a satisfyingly active state.

Inexhaustible forms of supplementary activities serve this aim. Absolute dominance of a fully satisfying professional drive and the acquisition of well-chosen supplementary drives are the conditions for a harmonious, well balanced life. Lack of full satisfaction in one's acquired professional and supplementary drives generates an urge to flee from frustration and seek salvation in 'Ersatz': smoking, alcohol, drugs, and so on.

TB: How did you study acquired drives in animals?

JK: In the early 1950s, we developed a method to show the development of an acquired drive, a "glass-cylinder-seeking drive," in the brains of rats that was stronger than the animal's innate drives. It was based on an unconditioned avoidance reflex, escape from a hot plate to the sound of a bell that played the role of a high priority conditioned stimulus. The cylinder was open at the bottom and on the top, and the animals were trained to search for the glass-cylinder, manage to get into the glass-cylinder through an opening of the side of the cylinder, and jump to the upper rim of the glass-cylinder. In properly trained rats, the acquired drive, cylinder-seeking drive, was so strong that it suppressed innate drives. When such a rat was deprived of food for 48 hours, and then was offered food within its usual setup that included the glass-cylinder, it looked for the glass-cylinder and left the food untouched, to the sound of the conditioned signal. Similarly, when a receptive female was offered to a glass-cylinder trained male rat, the male looked for the glass-cylinder to the sound of the bell and neglected the receptive female. With the employment of this method, it became obvious to me that cortical neurons have the innate potential to acquire a drive. With the help of our training method, we achieved that the rat mobilized, activated a group of cortical neurons that kept the animal active until the goal, the upper rim of the glass cylinder, was reached. The essence of both innate and acquired drives is a selective activation of a special population of subcortical neurons, that I refer to as an active focus, in case of innate drives, and of a special population of cortical neurons, in case of acquired drives.

TB: Did you succeed in developing acquired drives in all animals?

JK: The faculty for acquiring a drive is uncommon in the animal kingdom. It was shown by Berta Knoll, in the late 1950s, that the mouse, a rodent closely related to the rat, was unable to acquire the glass-cylinder-seeking drive. She has found that, in striking contrast to the rat, the mouse was even unable to fix the inextinguishable form of the conditioned avoidance response, the functional stage that preceded the acquisition of the glass-cylinder-seeking drive in the rat. It seems now that

the appearance of mammals with the ability to acquire drives was the last step in the development of the mammalian brain. Vertebrates can be divided into three groups according to the mode of operation of their brain: (a) those which operate with innate drives only (the majority), (b) those with an ability to acquire drives (a minority), and (c) the only one which operates almost exclusively on the basis of acquired drives (*Homo sapiens*). Thus, the appearance of the mammalian brain with the ability to acquire drives, ensured the development of social life, and ultimately, led to the evolution of human society. This most sophisticated form of organized life on earth is still in the trial-and-error phase of its development. It seeks to outgrow the myths-directed era of its history and arrive to its final state, the rationally directed human society.

TB: Coming back to your earlier remark, how did you record the corresponding EEG activity with an extinguishable- and an inextinguishable conditioned reflex?

JK: My coworker, Karoly Kelemen, spent half a year in Rome, in Bovet's laboratory, and finished the work showing the difference between the short lasting EEG activation to an extinguishable conditioned reflex, and the prolonged EEG activation to an inextinguishable conditioned reflex. The paper, co-authored by Kelemen, Longo, Knoll, and Bovet was published, in 1961.

TB: How did Bovet learn about your work?

JK: I published about six papers on my findings by 1956. Bovet read some of those papers and became interested in the research I was doing. At that time, Hungary was a communist country. We had the rats but no sophisticated machinery, not even EEG. We could do the EEG studies only in a laboratory, like Longo's, in Rome that was properly equipped.

TB: Vincenzo Longo, one of Bovet's collaborators?

JK: Yes. He is a very nice man; a good friend of mine. I have not heard of him for a long time. He has probably retired by now.

TB: He retired from the Institute but still works as a consultant.

JK: Longo understood very well what we were doing, and he had the necessary EEG technology to show the expected functional difference between an extinguishable- and an inextinguishable conditioned reflex.

TB: Did you, yourself, work on the neuronal level?

JK: I didn't at the time, but now I do, and measure, for example, the enhancer effect of drugs on noradrenaline release from the locus coeruleus, dopamine release from the substantia nigra, tuberculum olfactorium and striatum, and serotonin release from the raphe.

TB: So, by the 1960s, you became interested in enhancer mechanism and enhancer regulation by drugs.

JK: I was interested in understanding the physiological characteristics of an acquired drive. It was only later, in the course of my research with deprenyl that I ultimately recognized the operation of an enhancer regulation in the brainstem. This finding initiated the working hypothesis that the enhancer regulation operates also in the cortical neurons and determines, ultimately, the learning capacity of the individual.

TB: Could you elaborate on that?

JK: According to this approach, the naïve cortical neuron, which is born with the ability to perceive one of the senses: color, light, pain, sound, smell, taste, touch, is born with the ability to synthesize its own specific enhancer substance. Like PEA and tryptamine and their long-acting synthetic analogues, deprenyl and BPAP, respectively, enhance the activity of the enhancer sensitive brainstem neurons, the natural cortical enhancer substances act similarly on the proper cortical neurons. Since this working hypothesis was an outgrowth of deprenyl-research, it would be more expedient to come back to this approach after discussing the deprenyl-story in more detail.

TB: I see. As I remember from your recent studies, according to your present view, deprenyl is a synthetic, phenylethylamine derived enhancer.

JK: Yes. Deprenyl, the therapeutic agent now in use, is the minus isomer of phenylisopropylmethylpropargylamine, a close relative to methamphetamine, thus a derivative of PEA. Long acting PEA derivatives, like amphetamine and methamphetamine, release catecholamines from intraneuronal stores, as their parent substance, and produce aimless hyperactivity and inhibit goal directed activity of innate and acquired drives.

TB: Does that mean that by releasing catecholamines, these substances instead of enhancing, are inhibiting, innate and acquired drives?

JK: Amphetamine and methamphetamine are, of course, enhancer substances, but their releasing effect covers up completely the enhancer effect of these amines, which were classified as the prototype of indirectly acting sympathomimetics. I am not going into details; I was interested in

that. In 1960, I developed with a good friend of mine, Zoltan Meszaros, the director of research in Chinoin, a new family of analgesics. When I told my friend that I would be interested in finding someone who is working with amphetamines, he brought me together with Zoltan Ecsery, one of the leading chemists in Chinoin. At the time, iproniazid and monoamine oxidase inhibitors, in general, were in the center of interest as experimental tools because of their antidepressant effect. I worked with iproniazid, as soon as it became available, and I had the feeling that maybe somehow we have to combine amphetamine-like effects and MAO inhibition. So we started to work on that. As I was hoping, Zoltan Ecsery presented to me a series of about 60 compounds, and I selected from those compounds, as the best candidate for development, the compound that we call now deprenyl. At that time, it was called E-250. I selected it because I was fascinated by the finding that E-250, in contrast to the other monoamine oxidase inhibitors known at the time, did not potentiate the blood pressure increasing effect of amphetamine by releasing norepinephrine from their stores in noradrenergic terminals. In fact, when I gave E-250, it inhibited amphetamine's blood pressure increasing effect. That was new to me. It showed for me that here we have something new. This was it.

TB: To what did you attribute the uniqueness of E-250?

JK: You remember that in 1963, a calamitous number of clinical reports demonstrating the occurrence of dangerous hypertensive attacks in patients treated with MAO inhibitors were published. In accordance with Blackwell's suggestion, the metabolism of tyramine was inhibited by the MAO inhibitors and cheese and other foods containing tyramine provoked the hypertensive episodes in patients treated with MAO inhibitors. This 'cheese effect' restricted the clinical use of MAO inhibitors. We analyzed the peculiar behavior of E-250, and as I expected, the studies revealed that it did not potentiate the effect of tyramine but inhibited it. This was first demonstrated in a study performed on cats, and on the isolated vas deferens of rats which was published, in 1968. We proposed in this study to use deprenyl as a MAO inhibitor free of the cheese effect.

TB: How did you know that it applies also to human?

JK: In 1965, after we found that deprenyl, in contrast to other MAO inhibitors, inhibited the tyramine releasing effect of amphetamine, the psychiatrist Ervin Varga, who worked in the Psychiatric Clinic of our university, checked it out for me. He administered deprenyl and tyramine together to normal volunteers and found that deprenyl did not potentiate the effect of tyramine.

But he did not publish his results. As a matter of fact, the validity of my proposal that deprenyl is the MAO inhibitor free of the cheese effect was exactly demonstrated in humans by my good friend, Merton Sandler and his coworkers in London, in 1978.

TB: When did you publish first on E-250?

JK: The first paper appeared in Hungarian, in 1964, and the English version, in 1965. The paper was co-authored by my collaborators at the time: Ecsery, Kelemen, Nievel, and Berta Knoll. Then, in 1968, I published a second important paper on E-250 that was co-authored by Vizi and Somogyi, my other collaborators in this project. As I mentioned already, it was in this second paper that we noted that the cheese reaction, namely the hypertensive reaction seen in some MAO-inhibitor-treated patients after cheese consumption, is absent with deprenyl. We expressed, in our paper, that deprenyl, a MAO inhibitor without the cheese effect, maybe highly valuable for human therapy. But no one cared. Unfortunately even the leaders of Chinoin did not dare to develop further E-250 because of its MAO inhibitory potency.

TB: Didn't you already have in the title of your first paper that E-250 is a psychic energizer?

JK: We did. Actually the first clinical trial with racemic deprenyl in depression was done by Ervin Varga, my childhood-friend, my schoolmate in gymnasium, and class-mate at the university. The preliminary results were presented at a conference in Budapest, in 1965. The study was extended and was published by Varga and Tringer, in 1967. The first clinical trial with the minus isomer, the drug now in use, was published by Tringer, Haitis, and Varga, in 1971. In spite of their favorable findings, the possibility of introducing deprenyl as an antidepressant has remained unexploited for many years thereafter.

TB: One wonders why. Am I correct that we are still before the time that you discovered that E-250 is a selective MAO-B inhibitor?

JK: Yes, we are. Varga and Tringer published their first in extenso paper, in 1967, and we discovered E-250's selective B type monoamine oxidase inhibiting effect, in 1970.

TB: Could you elaborate on that discovery?

JK: In 1968, the same year our second paper was published, Johnston reported on a substance to be named clorgyline that preferentially inhibited the deamination of serotonin. He proposed the existence of two forms of the monoamine oxidase enzyme, a type A enzyme that is selectively inhibited by clorgyline and a type B enzyme that is relatively insensitive to clorgyline. Thus, a

selective MAO-B inhibitor was a missing pharmacological tool for further research. Because of the peculiar behavior of deprenyl, I expected that my substance might be the missing link. It was about two years after that, in 1970, that we were lucky to prove that deprenyl selectively inhibits the enzyme that was insensitive to clorgyline. Since Janos Nievel, who was responsible for the biochemical techniques in my laboratory, did not return from the study-tour I organized for him in London, where he spent a year in 1965, a young medical doctor, trained in biochemistry, Kalman Magyar, joined in the deprenyl-research. I published our finding that deprenyl is the selective inhibitor of MAO-B with Kalman Magyar, in 1972. This paper became a citation classic ten years later, in 1982.

TB: So, the paper was published about two years after the discovery.

JK: Yes. This paper was an *in extenso* publication of my lecture presented in the first international MAO meeting in Cagliari, Sardinia, in 1971. I first presented evidence in this meeting that deprenyl is a selective type B monoamine oxidase inhibitor. Then, I presented a lecture about the pharmacological effect of selective MAO inhibitors, in 1975, at the Ciba Foundation Symposium – “Monoamine Oxidase and its Inhibition” in London.

TB: Would it be correct to say that after you discovered that deprenyl is a selective inhibitor of the type B monoamine oxidase, your interest shifted to this particular effect of the drug.

JK: For several years the selective MAO-B inhibitory effect was at the center of our interest. It was the selective MAO-B inhibitory effect of the compound that led to the first clinical application of deprenyl.

TB: What was the first clinical application of deprenyl?

JK: In the light of the serious side effects of levodopa in Parkinson’s disease, Birkmayer and Hornykiewicz tried to achieve a levodopa sparing effect by the combined administration of levodopa with a MAO inhibitor. As such combinations frequently elicited hypertensive attacks, they were soon compelled to terminate this line of research. After we found that deprenyl is a unique MAO inhibitor that does not potentiate the catecholamine-releasing effect of indirectly acting amines, thus, it is free of the cheese effect, my claim was corroborated on human volunteers by Sandler and his group in London. When the results of this study came to the knowledge of Birkmayer, before it was published, he finally dared to combine levodopa with deprenyl in the treatment of Parkinson’s disease. The trial was successful. The levodopa-sparing effect was

achieved with deprenyl in parkinsonian patients without any hypertensive reaction. His report triggered a development that led to the world-wide use of deprenyl in Parkinson's disease.

TB: When did this happen?

JK: The Birkmayer paper, which triggered this development, was published in *Lancet*, in 1977.

TB: Deprenyl is still extensively used in the treatment of Parkinson's disease.

JK: Today, the most evaluated effect of the drug is its ability to slow the rate of functional deterioration of the nigrostriatal dopaminergic neurons in patients with early, untreated Parkinson's disease, and thus, to slow the progress of the disease. It is obvious by now that this effect is unrelated to the MAO-B inhibitory potency of deprenyl.

TB: So, your research on the type B monoamine oxidase inhibiting effect of deprenyl has paid off in the treatment of Parkinson's disease.

JK: Yes. The real progress in the clinical history of deprenyl was the establishment of the indication to use it in de novo parkinsonism. This was the conclusion of the famous DATATOP study in the USA, performed between 1989 and 1993. This indication was further supported by important multicenter studies, between 1991 and 1999, in France, Finland, Norway, and Denmark. The authors of the DATATOP study expected deprenyl to be efficient in their trial because of its MAO-B inhibitory effect. Their hypothesis was that the activity of MAO and the formation of free radicals predispose patients to nigral degeneration and contribute to the emergence and progression of Parkinson's disease. In accord with their working hypothesis, they expected that deprenyl, the MAO inhibitor, α -tocopherol, the antioxidant, and the combination of the two compounds will slow the clinical progression of the disease because MAO activity and the formation of oxygen radicals contribute to the pathogenesis of nigral degeneration. They selected patients with early, untreated Parkinson's disease and measured the delay of the onset of disability, necessitating levodopa therapy. When the DATATOP study started, I already knew from my studies that only deprenyl will be efficient in this study, because its peculiar stimulatory effect on the catecholaminergic system, of which α -tocopherol was devoid. Nevertheless, I was, at that time, only at the beginning of fully understanding the enhancer mechanism; but more and more experimental evidence accumulated in our work, which spoke definitely in favor of the concept that the peculiar deprenyl-induced activation of the catecholaminergic neurons is unrelated to its MAO-B inhibitory activity.

TB: What is the evidence that Deprenyl's enhancer effect is unrelated to MAO-B inhibition?

JK: With the development of 1-phenyl-2-propylaminopentane (PPAP), the deprenyl analogue free of the MAO-B inhibitory potency, we already furnished direct evidence that the enhanced dopaminergic activity following administration of deprenyl was unrelated to the inhibition of MAO-B. I published this paper, in 1992; my coworkers were Berta Knoll, Zoltan Torok, the chemist, who synthesized the compounds, Julia Timar, and Yasar Sevil. Because PPAP, like deprenyl, inhibited the uptake of tyramine in isolated smooth muscle tests, we first assumed that the drug-induced enhanced dopaminergic activity was due to an uptake inhibitory effect. Further studies revealed that this interpretation was false. The availability of HPLC to measure catecholamines and serotonin in physiological quantities allowed a new approach. The thorough analysis of the dose-dependent effect of deprenyl on the release of catecholamines and serotonin from isolated, discrete rat brain regions; dopamine from the striatum, substantia nigra and tuberculum olfactorium; noradrenaline from the locus coeruleus; and serotonin from the raphe, pointed to enhancer regulation in the mesencephalic neurons. Ildiko Miklya, a young talented pharmacist, was my coworker in these studies, demanding much hard work. We treated rats with five different doses of deprenyl, between 0.01 and 0.25 mg/kg, once daily for 21 days, isolated the discrete rat brain regions 24 hours after the last injection, and measured the biogenic amines released during a 20 min period from the freshly isolated tissue samples. The amount of dopamine released from the substantia nigra and tuberculum olfactorium clarified that the dopaminergic neurons worked on a significantly higher activity level, even in rats treated with the lowest dose of deprenyl, 0.01 mg/kg. As this small dose of deprenyl leaves the MAO-B activity and the uptake of amines practically unchanged, this study was the first unequivocal demonstration of the operation of a hitherto unknown, enhancer mechanism in dopaminergic neurons, stimulated by deprenyl, in very low doses. We published this work first with Ildiko Miklya, in 1994. This work was of crucial importance for further development of the enhancers. Further studies clarified the operation of an enhancer regulation in the catecholaminergic neurons in the brainstem and proved that PEA is a natural enhancer substance. Since PEA, in higher concentrations, is a highly effective releaser of the catecholamines from their intraneuronal stores, this effect covered up completely the enhancer effect of this endogenous amine, which was classified as the prototype of the indirectly acting sympathomimetics. Amphetamine and methamphetamine, PEA derivatives with

a long-lasting effect, share with their parent compound the releasing property. Deprenyl was the first PEA/methamphetamine derivative that maintained the enhancer effect of its parent compounds but lost completely the releasing property. This peculiar change in the pharmacological spectrum of this PEA-derivative, ultimately enabled the discovery of the enhancer regulation, since the enhancer effect of deprenyl was not covered up by the release of catecholamines from their intraneuronal stores. In light of this knowledge, we realized that clinicians who used deprenyl in the belief that the therapeutic benefits observed in patients treated with this drug were due to the selective inhibition of MAO-B in the brain, were mistaken from the very beginning. It is clear by now that besides the levodopa-sparing effect of deprenyl due to its MAO-B inhibitory potency, the clinical benefits are due to the enhancer effect of the drug.

TB: I see. We keep on talking about “enhancer regulation.” Could you tell us what the term “enhancer regulation” means?

JK: I define enhancer regulation as the existence of enhancer-sensitive neurons capable of changing their excitability and working on a higher activity level in a split second, due to endogenous enhancer substances. Of these substances, PEA and tryptamine are currently being experimentally analyzed, and their synthetic analogues, deprenyl and BPAP are the specific experimental tools for studying enhancer regulation in the brainstem.

TB: Where are those enhancer-sensitive neurons located in the brain?

JK: We usually refer to mesencephalic enhancer regulation because even if enhancer sensitive neurons exist also outside the mesencephalon, the mesencephalic dopaminergic neurons are of key importance in enhancer regulation. These, most rapidly aging neurons of the brain, are primarily responsible for the progressive age related decline of behavioral performances.

TB: Did you say that the mesencephalic dopaminergic neurons are the most rapidly aging neurons?

JK: According to our present knowledge, the nigrostriatal dopaminergic neurons are. The dopamine content of the human caudate nucleus decreases steeply, at the rate of about 13 percent per decade over age forty-five. We know that symptoms of Parkinson’s disease appear if the dopamine content of the caudate nucleus sinks below 30 percent of the normal level. The age related decline of the nigrostriatal dopaminergic brain mechanisms play a significant role in the

decline of performance with passing time. Safe and effective prophylactic medications are needed to slow these changes.

I suggested the use of deprenyl for this purpose after we found that treating rats with 0.25 mg/kg of deprenyl three times a week, prolonged their life significantly. It was my lecture at the Strategy in Drug Research, the 2nd IUPAC-IUPHAR Symposium held in Noordwijkerhout (The Netherlands), in 1981, when I first presented this new strategy. The lecture was published in the volume of this symposium, in 1982. We also revealed that deprenyl-treated rats lived not only longer than placebo-treated rats, but also that deprenyl-treated males maintained their ability to ejaculate for a significantly longer period and remained better performers in the shuttle box than their saline treated pairs. We followed through decades, with my coworker Janos Dallo, the sexual performance of male rats in longitudinal studies and found in series of experiments that a daily dose of 0.25 mg/kg deprenyl slowed significantly the age-related decline of this function. In one of this series, for example, we worked with 90 male CFY rats and treated half of the group with saline and half with deprenyl from the 25th week of age until they loss their ability to ejaculate. The saline-treated rats reached this stage at an average of 112 weeks, whereas the deprenyl-treated rats reached it at an average of 150 weeks. That deprenyl is capable of slowing the rate of functional deterioration of the nigrostriatal dopaminergic neurons was shown not only in rats, but also in patients with early, untreated Parkinson' disease. Age related deterioration of the striatal machinery is a continuum, and any short segment of it is sufficient to measure the rate of decline, in the presence or absence of deprenyl. Tetrad and Langston were the first to publish in *Science*, in 1989, that deprenyl delays the need for levodopa therapy. In their study, the average time that elapsed before levodopa was needed was 312.1 days for patients in the placebo group and 548.9 days for patients in the deprenyl group. This was clear proof that deprenyl, which enhances the activity of the surviving dopaminergic neurons, kept these neurons on a higher activity level for a longer duration of time. Today, the most evaluated effect of the drug is its ability to slow the rate of the functional deterioration of the nigrostriatal dopaminergic neurons in patients with early, untreated Parkinson's disease, and thus to slow the progress of the disease. The indication to use deprenyl in de novo parkinsonians was established in the USA by the Parkinson Study Group and was corroborated by a French Study Group, in 1991, a Finnish Study Group, in 1992, and a Norwegian-Danish Study Group, in 1999.

TB: Let me ask you about the naturally occurring enhancer substances, like PEA, that are usually classified as indirectly acting sympathomimetic drugs.

JK: As we discussed already, since PEA, in higher concentration, is a highly effective releaser of catecholamines from their intraneuronal stores, this effect covered up completely, for some time, the enhancer effect of this endogenous amine. Deprenyl was the first PEA derivative that maintained the enhancer effect of the parent compound but lost completely the catecholamine releasing property. It was this peculiar change in the pharmacological profile of this PEA-derivative that ultimately enabled the discovery of enhancer regulation in the catecholaminergic neurons in the brainstem, since the enhancer effect of deprenyl was not covered up by the release of catecholamines from their intraneuronal stores.

TB: You mentioned that not only PEA but also tryptamine is a natural enhancer substance.

JK: It was, in 1994, that I first published that tryptamine is also an endogenous enhancer. It is a natural enhancer like PEA but not a releaser. The discovery opened the way for a structure activity relationship study aiming to synthesize a new family of enhancer compounds structurally unrelated to PEA and the amphetamines. It was on the basis of the results of that study that benzofuran-propylaminopentane, BPAP, was selected as a tryptamine-derived synthetic mesencephalic enhancer. Because I couldn't get the work done in Hungary, I found a small Japanese private company, Fujimoto, to develop it. Professor Yoneda, an excellent chemist led the group which synthesized about 60 compounds and I selected the highly potent and selective enhancer, needed for my further work. BPAP was 100 times more potent than deprenyl as an enhancer. My first paper, co-authored by Yoneda, Berta Knoll, Ohde, and Miklya was published in the British Journal of Pharmacology, in 1999. A new world was opened! This new substance stimulates, activates, and enhances the activity of the noradrenergic, the dopaminergic, and serotonergic neurons in femto/picomolar concentrations, in a very special manner with a bell shaped curve. Now this indicates that very specific receptors, enhancer receptors, have to exist because otherwise we cannot explain a compound acting in femto/picomolar concentration. And now, something came about which I have to tell you. Towards the end of the last year, they found a gene of a totally independent family of receptors that are activated by PEA and tryptamine, the two endogenous enhancers which I described. It was published in the proceedings of the neuroscience meeting of the United States. This might be very important for the future. I think BPAP, the new compound,

which is, at present, a highly specific and highly potent experimental tool for studying the enhancer regulation in the brainstem, might also become, in the future, very important clinically as an antidepressant, an anti-Parkinson drug, and as an anti-Alzheimer's agent, and hopefully be also a safe and effective compound to slow the age-related decline of the catecholaminergic system in the brainstem, thus prolonging life span.

TB: What you are saying is that enhancers might have a broad range of clinical indications.

JK: Absolutely. In my view, the only reasonable hope to fight off the two main neurodegenerative diseases, Parkinson's and Alzheimer's, is prevention. In case of Parkinson's disease, there is no doubt that the age-related irreversible deterioration of the nigrostriatal dopaminergic neuronal system has already surpassed a critical level in patients, and the disease is incurable; prevention remains the only chance for the future to fight off Parkinson's disease. The daily administration, from sexual maturity until death, of a small dose of a synthetic enhancer substance acting on the dopaminergic neurons in the brainstem presents itself as a proper and a safe method for reaching this aim. In case of Alzheimer's disease, the only reasonable hope to fight off the disease is to keep the cortical and hippocampal neurons at a higher activity level as long as possible by the prophylactic administration of a proper enhancer substance. It is remarkable, in this regard, that BPAP protected cultured rat hippocampal neurons from the deleterious effect of 25-35 fragments of β -amyloidin as a low as 10-15M concentration.

TB: What about your longevity studies, demonstrating that deprenyl-treatment extended significantly the lifespan of rats?

JK: We performed two longevity studies in rats, the results of which were published in 1988 and 1994, respectively. Look, if you compare the average life expectancy in 1900 to the average life expectancy in 2000 in developed countries, there was for sure, at least, a 25 year extension. Average life expectancy at birth increased from about 55 years to 80 years. Why? The reason is that many people died earlier before the introduction of immunization, before the development of antibiotics, lack of hygiene, and many other factors. But, regardless of life expectancy, each species of animal has a natural life span that cannot be exceeded. You remember that according to the Old Testament, Moses lived 120 years. This is, by chance, in accord with the human Technical Life Span (TLSh), which is, in fact, about 115 to 120 years. It did not change from 1900 until 2000. Why? Because we had no knowledge about what regulates it. What I'm proposing is that

the age-related decline in the enhancer regulation of the catecholaminergic system in the brainstem is of key importance to natural life span, and to slow this process by the preventive administration of a proper synthetic enhancer will extend lifespan. As I summarized the physiological and pharmacological evidence in an invited paper “Memories of my 45 years in research” in *Pharmacology and Toxicology*, in 1994, there can be little doubt that the maximum level of activation of the CNS via the catecholaminergic system, decreases progressively with the passing time in aging. The blackout, natural death, of the integrative work of the CNS, signaled by the disappearance of EEG, occurs when the catecholaminergic system’s ability to activate the higher brain centers sinks below a critical threshold and the CNS can no longer be activated to the required extent. This would explain why a common infection, a broken leg, or any other challenge that is easily surmountable in young age, while the catecholaminergic machinery is working at full capacity, may cause death in old age. My hypothesis is that the quality and duration of life rests upon the inborn efficiency of the catecholaminergic brain machinery; a high performing, longer-living individual has a more active, more slowly deteriorating catecholaminergic system than a low performing peer; a better brain engine allows better performance and a longer life span. We succeeded, already, to demonstrate in rat experiments that the age-related decline of the catecholaminergic system in the brainstem, which starts immediately after sexual maturity, plays a key role in the natural aging of the brain, and the rate of decline can be slowed by the life-long daily administration of 0.25 mg/kg deprenyl. Deprenyl treated rats lived significantly longer and maintained their sexual potency and learning ability for a significantly longer duration of time than their saline-treated peers. Thus, it is feasible to transform a lower performing, shorter living rat into a better-performing, longer-living one. It, therefore, follows that the duration of life beyond the “technical” life span, with a yet unpredictable upper limit, must be possible in all mammals, including the human species, keeping the catecholaminergic system in optimal operation by the administration of a very small daily amount of a proper enhancer substance.

TB: Was deprenyl the first substance in the literature that was shown to prolong life span?

JK: Deprenyl was the first compound described in the literature that by curbing the age-related deterioration of the nigrostriatal dopaminergic neurons in the brainstem, prolonged the lifespan in the rat significantly, and some of them exceeded the technical lifespan. I showed this in two papers, published in *Mechanisms of Ageing and Development*: “The facilitation of dopaminergic activity

in the ageing brain by (-)-deprenyl: a proposal for a strategy to improve the quality of life in senescence” (1985); and “The striatal dopamine dependency of lifespan in male rats: longevity study with (-)-deprenyl” (1988). After publishing our first longevity study with my coworkers Janos Dallo and Tran Ty Yen, in 1989, I became interested to see whether the highest performing rats, selected from a huge population, live significantly longer than their lowest performing peers and whether deprenyl-treatment will evenly extend the lifespan of both groups. Thus, in my second study that lasted over four years, the results of which I published with my coworkers Tran Ty Yen and Ildiko Miklya, in 1994, I had 1600 male, healthy rats from a special strain. We tested their sexual activity by bringing them together with receptive females in four consecutive weekly mating tests. On the basis of their sexual performance, we separated the lowest and highest performing individuals. The selection from such a huge population was extremely tiring, boring work. Then, we measured the learning performance of the selected two groups of rats in five-day shuttle box training. We found that the sexually high performing rats were significantly better learners than their sexually low performing peers. In the four years study, we also found that the high performing rats lived significantly longer than the low performing ones. The low performing rats lived 134 weeks, while their high performing peers lived 151 weeks. In low performing and high performing rats, deprenyl, an enhancer of the release of catecholamines in the brain, significantly increased sexual performance and longevity. The lifetime of deprenyl-treated low performing rats increased from 134 to 152 weeks, and of high performing rats from 151 to 185 weeks. The increases in longevity were statistically highly significant. So, the enhancer really increased sex, learning ability, and duration of life. This applies also to man. In Hungary, for example, millions die at age 62 or 63 now, but if you compare that with the age of the members of the academy, you will see that their average age at the time of death is 81.5 years. What I’m saying, is that a man who works, who is active, lives longer than a passive one. I work a lot, although I am now retired. I could just look at the television. So people ask me “why are you going at 8:00 AM in the morning to your laboratory and come home at 6:00 PM, like in your youth, and then you are working until 2:00 a.m. on your papers at home. Are you crazy?” I’m not crazy. The conclusion of my lifework is that the longer you keep your brain on the maximum activity, the longer and better you live. What I’m saying, is that what we have shown in the rats, applies also to human. I’m 77 now. In the 20th century, we have seen a highly significant change, an increase in average

life expectancy. But by affecting enhancer regulation, we should be able to prolong life span further, and sometimes in the future surpass significantly the TLSh. Enhancer regulation is the key to life and death.

TB: Would it be legitimate to hypothesize that if one would get a bunch of 30 years old guys, measure their sexual activity, and if it is high, one could predict that they would live longer?

JK: Man is complicated. It is the optimal condition for the human brain to work under the influence of an acquired drive, which is in harmony with one's natural endowments. It is reasonable to assume that for a human being, the optimal condition is to be in a state in which a group of cortical neurons are permanently maintained by their specific enhancer substance at the highest level of excitability. The essence of this mechanism is detectable, even in animals, capable to acquire drives. Whoever built an acquired drive into the brain of a dog, experienced the animal's extreme joy in exercising the acquired goal-seeking activity and also witnessed that the animal spares no effort to reach the goal. Humans know from their experience that they prefer to be in an active state that is pleasant, amusing, that makes them happier and more satisfied than to be in the vigilant leisure state. It is natural for humans in possession of a proper work-related drive that their preferred activity never makes them tired. Creative minds demonstrate this physiological endowment of the human brain most convincingly. Mozart wrote once to his father, that to compose music is the rest for him, and the inability to do so, immediately tires him. Millions and millions in possession of a proper work-related drive could have written this letter.

TB: Where do you measure enhancer effects in the brain?

JK: Since catecholaminergic and serotonergic neurons are enhancer sensitive neurons and we demonstrated that PEA and tryptamine are natural enhancer substances acting on these neurons, their long-acting analogues, deprenyl and BPAP, respectively, are now the proper experimental tools to study the enhancer regulation in the brainstem neurons. In contrast to deprenyl which is an enhancer of the catecholaminergic neurons and almost ineffective on the serotonergic system, BPAP is a highly potent enhancer of the serotonergic neurons too. As a matter of fact, BPAP is, at present, the most selective and potent experimental tool to investigate enhancer regulation in the catecholaminergic and serotonergic neurons in the brainstem. I just finished a paper, coauthored by Ildiko Miklya and Berta Knoll, which I am going to send to Life Sciences, analyzing in more detail that a bimodal, bell-shaped concentration effect curve is characteristic of the

enhancer effect of both deprenyl and BPAP. BPAP acted, for example, on isolated locus coeruleus of rats in a manner that we found a peak-effect at 10^{-13} M concentration and a second peak at 10^{-6} M concentration. It is obvious that the specific enhancer effect is the physiologically relevant one. Interestingly, at 10^{-10} M concentration, we were unable to detect the enhancer effect. We measured also the BPAP-induced enhancement of noradrenaline release from the locus coeruleus 30 min after the subcutaneous administration of a single dose of BPAP and found the same characteristic dose-dependency of the enhancer effect. For example, the most effective dose of BPAP, 0.0005 mg/kg, increased the release of noradrenaline from 4.7 nM/g (control) to 15.4 nM/g, but a 100 times higher dose of BPAP (0.05 mg/kg) did not change it.

TB: This a very strange, unusual form of dose-dependency, isn't it?

JK: It is. But, it seems to me that this peculiar form of dose-dependency is of high physiological significance. It allows giving a reasonable explanation for the substantial individual differences found in behavioral performances. Since an optimum concentration of the enhancer substances was needed for the optimum performance, I postulate that the substantial individual differences found in behavioral performances are due to the peculiar dose-dependency of the presently still unknown natural cortical enhancer substances. This approach grants us new perspective on the results of our two longitudinal studies in rats. As an example, let me analyze our second longitudinal study in rats from this perspective. This study was performed between 1990 and 1994. As I mentioned earlier, we started working with a random population of 28-week old male rats and tested their sexual performance once a week. Rats representing the two extremes in performance were selected for the study: ones that did not display a single intromission during the four consecutive weekly-mating tests used for selection, and ones which showed full scale sexual activity (mounting, intromission, ejaculation) in each of the four tests. Out of 1600 sexually inexperienced 28-week-old Wistar-Logan male rats that met a receptive female once a week for 4 consecutive weeks, 94 did not display a single intromission during the selection period and 99 displayed at least one ejaculation in each of the four tests. The former were taken for the sexually lowest performing (LP) rats and the latter for the highest performing (HP) ones. Considering the unique, dose-related effect of an enhancer substance, it is reasonable to assume that out of the 1600 rats the 99 HP rats produced their endogenous enhancer substances at the peak of the bell-shaped concentration/effect curve, while the 94 LP rats produced them at the least active part of the curve;

and the production of the overwhelming majority of the population, 1407 rats, fall between the two extremes.

TB: Are enhancer substances neuroprotective agents?

JK: It is obvious that an enhancer substance acts as a neuroprotective agent on enhancer sensitive neurons. To illustrate it, let us analyze our first study on the neuroprotective effect of BPAP on cultured rat hippocampal cells. To elicit cell death, the cultured hippocampal neurons were treated with the 25-35 fragment of β -amyloid. BPAP exerted its enhancer effect in its characteristic bipolar manner with bell shaped concentration-effect curves. The peak effect was reached at 10^{-14} M, in the low femto/picomolar concentration range, and at the high 10^{-8} M concentration. Because of the neurotoxic effect of β -amyloid25-35, no more than 20 per cent of the cells, obviously the high performing cells, survived this attack. As BPAP significantly enhanced the performance of the neurons in the culture, in the presence of the optimum concentration, i.e., 10^{-14} M of BPAP, about 70 percent of the cells survived. We published these findings, in 1999. We also published that BPAP enhanced the activity of the catecholaminergic and serotonergic neurons in isolated discrete midbrain regions in exactly the same bipolar manner and in the same concentration range. The studies with BPAP, performed on noradrenergic, dopaminergic, serotonergic, and hippocampal neurons, proved unequivocally the operation of a highly specific, complex form of enhancer regulation in sub-cortical neurons. This is very much in keeping with the ascription of a commanding role to midbrain neurons in goal seeking behavior.

TB: So, there is a highly specific form of enhancer regulation in sub-cortical neurons.

JK: The sub-cortical system is the place of the innate drives in the service of the limited number of vital goals, sexual activity, feeding, nurturing. But, as I told you, humans are the only living beings on earth whose life is predominantly based on acquired drives.

TB: Did you test already the effect of your enhancer substances on cultured cortical neurons?

JK: The first study of the enhancer effect on cultured cortical neurons was performed with BPAP on a primary culture of rat cerebral cortex. It was done by the Japanese and showed that BPAP significantly protected cortical neurons against serum-free-condition induced cell death in the high concentration range. However, in striking contrast to the finding on cultured rat hippocampal neurons, BPAP did not exert an enhancer effect on the cultured rat cortical neurons in the femto/picomolar concentration range.

TB: So, BPAP in the low concentration range has no effect on cortical neurons.

JK: The reason of this finding is now clear. BPAP acts on the enhancer-sensitive sub-cortical neurons, but it is ineffective on cortical neurons.

TB: What is the experimental evidence for your statement that BPAP has no effect on cortical neurons?

JK: To test a compound's ability to enhance the acquisition of a conditioned avoidance reflex (CAR) in the shuttle box, it is necessary to select proper training conditions. In the case in which the rat was trained with 100 trials per day, the acquisition of CARs reached an 80% level. To demonstrate the highly significant enhancer effect of BPAP on sub-cortical catecholaminergic neurons in vivo, we trained the rat with 100 trials per day, blocked the acquisition of CARs by pretreating the rats with tetrabenazine, and restored the learning ability with the simultaneous administration of BPAP. Learning is a cortical function. In the series of experiments aiming to test the effect of BPAP on cortical neurons, we trained the rats with 20 trials per day in order to have a chance to detect the drug-induced improvement in the learning ability realized via the direct stimulation of cortical neurons. The percentage of CARs in rats trained with 100 trials per day was 77% on the 5th day of training. In contrast, it was only 8.5% in rats trained with 20 trials per day. Thus, in case BPAP had possessed a specific enhancer effect on cortical neurons, we could detect easily in form of a significant, dose-dependent increase in the percentage of CARs in rats trained with 20 trials per day. Because of the bell-shaped concentration effect curve characteristic of the enhancer effect of BPAP, we used 10 doses of the compound, ranging from 0.000001 to 10 mg/kg, to clarify the effect of BPAP on the cortical neurons. None of the applied doses of BPAP was capable of changing the learning performance of rats in the shuttle box. Thus, in accord with the findings on cultured rat cortical neurons, the in vivo experiments confirmed that BPAP, the presently known most potent enhancer of the sub-cortical catecholaminergic neurons, is devoid of a specific enhancer effect on the cortical neurons.

TB: I see. You say that BPAP activates the cortical neurons only via the enhancement of the catecholaminergic system in the brainstem?

JK: Exactly. And now I'm coming back to my earlier mentioned, but unexplained, working hypothesis, catalyzed by the discovery of the enhancer regulation in the brainstem, that learning is a cortical enhancer-regulation-dependent function. My concept is that learning needs only the

concurrent operation of functionally different groups of cortical neurons under proper conditions. In vertebrates, learning - the modification of behavior through practice, training, or experience, one of the essential necessities of life - is the main physiological function of the cortex. Modification of behavior rests upon the inborn ability of cortical neurons to get acquainted with each other through training, learn to influence each other's function, and cooperate thereafter according to the need. The mechanism of this important process is, however, still unknown. The discovery of the enhancer regulation offers the following interpretation of learning. Each member of a population of naive cortical neurons (Group 1) born to perceive a specific quality of stimuli, originating from outside or inside the body, synthesizes the same enhancer substance. It is also supplied with enhancer receptors to which this enhancer substance is the highly specific ligand. The stimulation of the neurons with their enhancer substance leads to enhanced excitability. On the other hand, each cortical neuron is able to activate under proper conditions (training) an enhancer receptor to any of the existing cortical enhancer substances (learning). Thus, neuron A is born with its specific enhancer receptor (ER_A) and with the ability to synthesize its own enhancer substance (ES_A). Neuron B is born with ER_B and synthesizes ES_B , and so on. Whenever a cortical neuron gets excited, its specific enhancer substance is synthesized in an increased amount, and its sensitivity toward other enhancer substances is significantly increased. When neuron A and B are simultaneously stimulated, both are continuously bombarded with a higher amount of the enhancer substance of the other neuron and at the same time also sensitized to activate a receptor to the alien enhancer substance. As a consequence, the concurrent stimulation of neurons A and B time after time (training) ultimately leads to the fixation of a new functional constellation. Neuron A acquires sensitivity toward ES_B , and neuron B acquires sensitivity toward ES_A . Thus, learning means that a neuron acquires the ability to respond to originally alien stimuli. As a consequence of this change we experience the training induced modification of behavior.

TB: What is the experimental proof supporting this new concept?

JK: Using the shuttle box technique, there is a reasonable possibility of testing the validity of this concept on rats. The shuttle box is a simple and useful setup for following the development of a two-way conditioned avoidance reflex (CAR). The box is divided inside by a barrier with a small gate. The rat is trained to cross the barrier under the influence of a flash of light (conditioned stimulus, CS). If the rat fails to do so, the animal is punished with an electric foot shock

(unconditioned stimulus, US). The rat is trained with 100 trials/day. One trial consists of 15s intertrial interval, followed by 15s light flash that overlaps with a foot shock for 5s. The rat learns to avoid punishment and escapes in response to light flash within 10s (CAR). This is automatically counted. According to present views, the rat, driven by fear, tries to prevent punishment and learns by trial and error to escape, in due time. The efficiency of learning is thought to be proportional to the number of the successful crossings in response to light flash within 10s. According to our new concept, the efficiency of learning depends on the repeated simultaneous operation of functionally different populations of cortical neurons. In light of this approach, we need to weigh carefully the series of events in the cortex during the training procedure. The concept predicts that the development of a stable CAR in the shuttle box signifies the acquisition of a special cooperation between the groups of cortical neurons born to perceive the foot shock (US) and the light flash (CS), respectively. Nevertheless, other groups of cortical neurons, stimulated by the setup as a whole, are also involved in the special modification of the rat's behavior. In the course of training numerous groups of cortical neurons, A, B, C... n, born to perceive special information only, are synchronously active and influence each other. Furthermore, each group of neurons has chance to develop sensitivity toward each of the enhancer substances belonging to the simultaneously activated groups of neurons. Thus, during the training procedure, a network of co-operating groups of cortical neurons develops, which operates, thereafter, as an entity. The training-induced cooperation between the groups of neurons can be 1) transient in nature (chain of extinguishable conditioned reflexes, ECRs), 2) irreversibly fixed (chain of inextinguishable conditioned reflexes, ICRs), or 3) may lead to the development of the most sophisticated form of excitatory state in a group of cortical neurons ('active focus') that will operate thereafter as an acquired drive. However complicated the cooperation developed between different group of neurons during training may be, it is their common feature that they work thereafter as an integral whole, and this entity can be activated via a few decisive groups of neurons. Thus, my approach is that the modification of behavior of the rats trained in the shuttle box depends on the synchronous activation of different groups of cortical neurons in the brain for a proper period of time.

TB: I see. What is exactly your method to test your concept in rats?

JK: Treatment of rats with 1 mg/kg tetrabenazine, which blocks selectively and reversibly the reuptake of the catecholaminergic transmitters into their intraneuronal stores, depletes

noradrenaline and dopamine from the end organs of the catecholaminergic neurons in the brainstem. Since the operation of the catecholaminergic brain engine is the condition sine qua non for the trial and error mechanism, thus for the success of reaching a goal, the acquisition of a CAR in the shuttle box cannot be detected in tetrabenazine-treated rats because of the blockade of the animal's ability to cross the barrier. Nevertheless, the activation of the cortical neurons via the unconditioned- and conditioned stimulus remains unchanged in tetrabenazine-treated rats. The experiments are now in progress; let me mention my first results. I treated rats with tetrabenazine, which as I mentioned already, blocks the catecholaminergic engine of the brain without acting on cortical neurons. I am using a strain of rats with exceptionally low learning capacity and work with females, which are lower performers in the shuttle box than their male peers. I am testing the rats daily in the shuttle box, from Monday until Friday with 100 trials/day. One group is treated subcutaneously with saline; the other group with 1 mg/kg tetrabenazine. The saline-treated rats developed, of course, a stable conditioned avoidance reflex. Because we work with a dull strain of rats, on the first day of training, lightflash, the conditioned stimulus, was only an average of 10% effective in eliciting the escape of the rats to the other part of the compartment within 10 seconds. On the 5th day of training, 79% of the rats escaped in response to the lightflash. However, even on the 5th day of training, less than 5% of the tetrabenazine treated rats escaped in response to the light flash. After the 5-day-training period, both the saline and tetrabenazine-treated rats had a rest on Saturday and Sunday. This resting period is enough for the complete elimination of tetrabenazine. On Monday, we again tested the animals and found that 81% of the saline-treated rats and 65% of the rats treated with tetrabenazine during the training period, escaped in response to the light flash. You remember that only 10% of saline treated rats of this dull strain escaped on the 1st day of training in response to the lightflash. Now, despite of the fact that the tetrabenazine-treated group of rats did not show any sign of the acquisition of a CAR during the 5-day training, in fact they fixed the CAR in their cortex, since after the elimination of tetrabenazine, 65% of the rats escaped in response to the light flash. This finding is in accord with the concept that learning needs only the concurrent operation of functionally different groups of cortical neurons under proper condition.

TB: The astonishing results of this experiment are really thought provoking and seem substantially supporting your working hypothesis that learning might be an enhancer-dependent cortical

function. But, be that as it may, it will for sure initiate much work in this new direction. What about the recent finding that BPAP exerts an enhancer effect also on neuroglial cells?

JK: Neuroglial cells, play an important physiological role in the brain, and modulate the function of neurons in a complex manner, but they do not participate in the realization of drive dependent, goal-seeking behavior. Our Japanese collaborators used astrocytes in their research and measured the rate of synthesis of three neurotrophic factors, the nerve growth factor—NGF, the brain-derived neurotrophic factor—BDNF, and the glial cell line-derived neurotrophic factor—GDNF and found that BPAP in the micromolar concentration range increased significantly the synthesis of neurotrophic factors, but we found, in a series of experiments now in progress, that BPAP is ineffective on glial cells in the low femto/picomolar concentration range. Thus, the specific form of enhancer regulation is not detectable in the glial cells. These findings support the view that the specific form of enhancer regulation stimulated by BPAP in the extremely low concentration range is the behaviorally important form, whereas the enhancer effect of BPAP in the micromolar concentration range is insignificant in behavioral terms. Nevertheless, the finding that BPAP-induced enhancement in the synthesis of neurotrophic factors in the micromolecular concentration range is a remarkable pharmacological effect, whose therapeutic value deserves further analysis in the future.

TB: Am I correct that you have done all your research in the Department of Pharmacology at Semmelweis University in Budapest?

JK: Yes. I started my career in the department as a medical student, in February 1949, and I never left it in my life.

TB: Since the time you published your first book on “The Theory of Active Reflexes,” more than 30 years have passed.

JK: As a matter of fact, to the end of 1953, I already developed and studied in detail the technique to analyze in rats the acquired drive and my theory that I summarized in this monograph was basically completed 16 years earlier. I needed 30 years, thereafter, to get to the core of the acquired drives and realize that the root of the matter is the enhancer regulation in the brainstem and in the cortex. As we already discussed, enhancer-sensitive neurons in the brainstem and in the cortex are, in my view, capable of changing their excitability in a split second and working as needed at a

higher activity level. I have already started to summarize my neurochemical concept of innate and acquired drives in a new monograph.

TB: You mentioned earlier that the antidepressant effect of deprenyl was shown, but not fully explored. Could you elaborate on that?

JK: It was Varga who first described the antidepressant effect of deprenyl, in 1965, and published with his coworkers two more papers, in 1967 and 1971, extending their results. Then later in the '80s, Mann and Gershon, Mendlewicz and Youdim, Quitkin and his associates, and McGarth and his collaborators have provided further substantiation that deprenyl is an antidepressant. Unfortunately, no big drug company picked it up and up to the present, deprenyl was nowhere registered as an antidepressant. It might happen in the future and BPAP is also from this aspect a promising compound.

TB: Do you think that enhancer substances have antidepressant effects? The diagnosis of major depression refers to a clinically and pharmacologically very heterogeneous population.

JK: BPAP, which is a selective enhancer substance, stimulates the catecholaminergic and serotonergic neurons in the brainstem via a previously unknown mechanism. Because it is a highly potent compound, there is good reason to believe that it will be used sometimes in the future as a valuable antidepressant.

TB: Regardless what happens with BPAP and enhancer regulation, you developed deprenyl, the first MAO-B inhibitor and this alone is a major contribution to the field of neuropsychopharmacology. Was this research followed up? Are there any other MAO-B inhibitors?

JK: Well, there are, but insofar as I know, none of them is comparable to deprenyl in its effect in Parkinson's disease.

TB: When did you start with the development of BPAP?

JK: It started in the early '90s.

TB: How did you get to the idea to develop BPAP?

JK: I wanted to develop a selective enhancer substance which is unrelated to phenylethylamines and is devoid of MAO inhibitory potency. I firmly hope that in the long run, BPAP will ultimately convince the scientific community that enhancer regulation in the brain is a mechanism of key

importance and drugs which stimulate selectively this mechanism are of significant therapeutic value.

TB: Is there any relationship between your anti-aging drugs and the late Giurgea's nootropics?

JK: Nootropics have nothing to do with enhancer regulation. Since we have now the specific method for measuring quantitatively the enhancer effect of a compound on the locus coeruleus, striatum, substantia nigra, tuberculum olfactorium, and raphe, we tested, just recently, on these isolated discrete rat brain regions the effect of piracetam in a wide dose-range. We found that this prototype of nootropics, Giurgea's original substance, is devoid of an enhancer effect.

TB: Could we switch now to more personal matters in your life. You told us that you joined the department of pharmacology after your third year in medical school.

JK: I started to work in February in 1949 as a student and graduated from medical school in 1951.

TB: Could you tell us about the Department of Pharmacology at Semmelweis University. Isn't it one of the oldest pharmacology departments in the world?

JK: Since the first pharmacology department in the world was founded, in 1849, in Dorpat (Germany), now Tartu in Estonia, and our department was founded in 1872; it is really one of the oldest. Its first chairman was Kalman Balogh. He was followed by Arpad Bokay, Zoltan Vamossy, and by my predecessor, Bela Issekutz. I succeeded Issekutz in 1962. I was the fifth chairman of the department. I retired from my chair in 1993, after 31 years. But I remained fully active as a member of the Hungarian Academy of Sciences and continued with my research. I was chairman of the department longer than any of my predecessors.

TB: So, you are an active member of the Hungarian Academy of Sciences.

JK: Yes, I am. Each of my predecessors was a member of the Academy and I have continued in that tradition. I became a corresponding member of the Hungarian Academy of Sciences, in 1970, when I was 45 years old, and a full member in 1979. In 1970, I was the youngest member of the Medical Class of our Academy, and now I'm one of the oldest.

TB: I remember your 60th birthday was remarkably celebrated.

JK: I got, in 1985, the National Prize, the highest honor given for scientific achievement in Hungary. The birthday celebrations at the Academy, and thereafter, in the Institute were touching events. I was honored with a Festschrift: 'Neuropharmacology 85'. Eds. Kelemen K, Magyar K, Vizi ES, Publishing House of the Hungarian Academy of the Sciences. Budapest, 1985 (351

pages), containing 49 papers of distinguished scientists from all over the world. I was honored also on my 75th birthday with a Festschrift: Milestones in monoamine oxidase research: discovery of (-)-deprenyl. Eds. Magyar K, Vizi ES, Medicina Publishing House, Budapest, 2000, (251 pages).

TB: What about your relation to foreign Academies and Universities?

JK: I was honored, in 1974, to become a member of the Leopoldina Academy of Natural Sciences, one of the oldest academies in the world. In 1984, I received an honorary doctorate from the Medical Academy of Magdeburg, and in 1989, I was honored with honorary doctorate from Bologna University on the occasion of its 900th year anniversary. Since Bologna University was the first in the world, I feel this honor a privilege. In 1990, I was elected Honorary Fellow of the Royal Society of Medicine (London), and in 1995, I became foreign member of the Polish Academy of Arts and Sciences.

TB: Have you been active in professional societies?

JK: Traditionally, pharmacologists were everywhere in the world members of their national physiological societies which were members of the International Union of Physiological Sciences (IUPS). The rapid development of pharmacology made it clear to the end of the 1950s that time was ripe for the creation of independent national pharmacological societies and the International Union of Pharmacology (IUPHAR). But it was neither on the national level nor on the international level easy to break with the tradition. I started in Hungary the fight, in 1958, to attain our independence and we succeeded finally to establish very early, already in 1962, the Hungarian Pharmacological Society; I was the first executive secretary, and after Bela Issekutz, the second president; since 1983, I have been Honorary President of the Society for Life. IUPHAR was established in 1965; I was member of the Executive Board, from 1982 until 1984 as councilor, and from 1984 until 1987, as First Vice President. I was elected honorary member of the Pharmacological Societies of Poland (1980), Czechoslovakia and Bulgaria (1985), and the Austrian Parkinson Society (1986). I was honored with the Award for Distinguished Service in European Pharmacology (1999) and with the Award for Outstanding Contribution to AntiAgeing Medicine (2001).

TB: Would you like to mention just a couple of people you trained?

JK: I mention just those who worked with me through decades: Karoly Kelemen, Berta Knoll, Janos Dallo, Kalman Magyar, Szilveszter Vizi, Zsuzsanna Furst, Tamas Friedman, Klara Gyires, Huba Kalasz, Valeria Kecskemeti, Julia Timar, Zsuzsa Gyarmati, and Ildiko Miklya.

TB: Is there anything else you would like to mention?

JK: You can see two large leather bound volumes there on my bookshelf. I received those volumes on my 50th birthday, in 1975, from my co-workers. Reprints from our numerous publications during my first 13 years as head of the department are bound in those two volumes. One would need at least 10 such volumes to include a reprint of all our publications from the 31 years I was chairman of the department.

TB: And you are still fully active.

JK: Oh, yes. I am fully active in research, but I retired from my administrative positions. Zsuzsanna Furst, one of my pupils is now the head of the department.

TB: Besides being chairman of the department of pharmacology, did you have any other administrative position?

JK: I was from 1964 until 1970, the Vice President of the University responsible for research, and the Vice President of the Medical Class of the Hungarian Academy of Sciences from 1967 until 1976. Apart from the Hungarian Pharmacological Society and IUPHAR, I never accepted thereafter any administrative position.

TB: What would you consider your most important contribution?

JK: From a practical point of view, the discovery of enhancer regulation and the development of synthetic enhancer substances, from theoretical point of view, the discovery that with the evolution of brains capable of acquiring drives, species appeared whose members could manipulate each other's behavior and act in concert. This was the condition sine qua non for the evolution of social living, a form of life that enabled the species to surpass qualitatively the performance of any given individual.

TB: On this note we should conclude this interview with Professor Joseph Knoll. Thank you for your contributions to neuropsychopharmacology and for sharing this information with us.

JK: I feel honored by having this interview. Thank you very much.

40. IRWIN J. KOPIN

TB: We are at the Acapulco Princess Hotel in Acapulco, Mexico. It is December 12, 1999. I will be interviewing Dr. Irwin Kopin⁴² for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let's just start from the very beginning. Where are you from?

IK: OK. I was born in New York.

TB: Where were you brought up?

IK: I was brought up in the Bronx. My first memories are of the Bronx, and then, we used to go away during the summer to Long Island. We had a small place in Rockaway, on the beach, and that's where I learned to swim. Swimming has been part of my life. My wife says that there are four S's in my life: swimming, science, stamps, because I collect stamps, and spouse, and she says, it better be spouse. In any case, Science started a long time ago. When I was about nine years old, I got a chemistry set, and this, actually, is why my wife married me, and the connection you'll see in a minute. I played with the chemistry set and I told my father, when I was about ten or eleven years old, that I wanted to be a chemist when I grew up. He responded: "You'll never be a chemist unless you know how to make a mirror." Well, my father had a factory that made mirrors. He was in the "mirror business," and I was intrigued by the idea that you could make a mirror with chemicals. I went to the public library and I read up on making mirrors. I found out that forming a mirror is a test for the identification of aldehyde. You take a silver nitrate solution and add ammonia to it. At first, you get a precipitate. Then, the precipitate dissolves. When a reducing agent, such as an aldehyde, is added, you get a mirror. I tried what I read and got a black precipitate with a little silver streak of a mirror along the side.

If you see that silver streak, you know that the silver has been deposited, and that's the way you make a mirror. Well, I showed this test tube with the black precipitate and the silver streak to my father and he said, "Do you think I could sell that for a mirror"? And, even I, an eleven year old, knew that you could never sell this black thing with a little silver streak as a mirror! So, I went

⁴² Irwin J. Kopin was born in New York, New York in 1929. He received his M.D. from McGill University and completed a residency in Medicine at Boston City Hospital. He spent the remainder of his career at the National Institutes of Health in the Intramural Programs of NIMH and NINDS. He was interviewed in Acapulco, Mexico on December 12, 1999.

back to the books and I read some more. This was over years. By the time I was fourteen, I had learned a good deal more chemistry. I went to the Bronx High School of Science, and during that period of time, I still persisted, and tried to make a mirror about thirty different ways.

I wrote to the Department of Commerce and asked them “How do you make a mirror?” They sent me a brochure that listed about a hundred ways of making a mirror. Over the years, before and after receiving the brochure, I tried about sixty of them. They would all give the black precipitate and a little bit of this silver streak. My father said, “At this rate you’ll never be a chemist. But at least, you should have a trade.” I was about sixteen at the time and was allowed to work. On weekends, he took me down to the factory, and I learned how to drill holes in glass. At that time, they used a tungsten carbide drill with water dripping on it to keep it cool and prevent glass powder from being inhaled. If you pressed too hard, the glass broke. If you didn’t press hard enough, you could sit there all day and you wouldn’t get a hole. But, after a while (it took about a seven days work), my father said I had “the touch.” I could drill one hundred and eighty holes an hour in the glass, but I hated to do it. It was boring. I didn’t know what to do during the boring task. I used to skip lunch, so I could go home early. When I told my father how I felt, he replied, “Well, you know, you’ll have to learn how to make a mirror.” So, one day, I went up to the person who was in charge of silvering glass to make mirrors and I told him about my experience. He said, “Oh, you have to wash the glass! If you have a little bit of grease or a little bit of dirt on the glass, that acts as a nidus for the black precipitate. You have to clean the glass thoroughly!” He then taught me how to clean glassware. First, use sodium hydroxide solution, then use distilled water to wash that out, then scrub with red copper oxide, cuprous oxide, then wash with more distilled water. Only after this wash, do you add the silver nitrate solution. When I did this at home, and I was able to bring a beautiful silver finger, like the inside of a thermos bottle, like a Dewar flask, to show my father, he said, “Oh, now you can go to college!” So, that was my entrée into college. And, I went to City College for two years, again with the idea that I probably would do something in chemistry. At about that time, however, I decided, I want to go to medical school. In those years, it was very difficult to get into medical school from City College. I decided that I had to transfer to a different college to be able to do it.

TB: What year was that?

IK: It was in 1948. About that time, my father wanted to bring to the United States my aunt, who had been in a concentration camp and was the only one of my father's five siblings who survived the Holocaust. However, she was unable to get a visa to enter the United States, but Canada was more receptive. So, my father arranged for her to go to Montreal and settle there. I was an only child and he knew that I had to get out of the house that I had to go off to college. But he didn't want me to be alone, cold, and hungry in a strange city without any relatives. So he convinced me, to go, with my good friend, Ruben Bressler, to McGill University in Montreal. Rube and I were friends (and still are) since second year high school and went to City College together. And, so, that's how I got to McGill. Well, in the organic chemistry course in McGill, Rube Bressler and I were lab partners. There were girls taking the same course, and of course, we knew them. In one of the laboratory exercises we had to make an aldehyde and test for the presence of aldehyde. Although we had done everything together, when it came time for testing for the aldehyde, I said, "Rube, you must step aside. I will do this." Of course, I cleaned the glassware thoroughly and got this beautiful silver finger of a test tube. We brought this to the instructor and he'd never seen one like that. He was used to seeing the black precipitate with the little silver streak on the side of the tube. So, when we gave him this test tube, he put it on exhibit in front of the class. The girl I was dating, Rita, was in the class, and she was so impressed with that that she finally agreed to marry me! That really was my first introduction of how important it is to wash glassware; the details of laboratory work were impressed on me very early. Years later, Julie Axelrod, with whom I worked at NIH, claimed that he used to get his best ideas washing his glassware. His laboratory work was mainly enzymology and it was important to have clean glass. He knew it. If I had known that when I was younger, I would have been able to convince my father earlier that I was college material. But, it was a very, very useful experience. At McGill, Rube and I majored in Biochemistry. Professor David L. Thompson, who was Chairman of the Department of Biochemistry, was a wonderful, inspiring lecturer. He used to come in to class with a small card and taught us everything from Nutrition to advanced Protein Physical Chemistry. Professors Orville Denstedt, Murray Saffran, and Judah H. Quastel constituted a great group of biochemists. After graduating from the Honors Course in Biochemistry, I went to McGill's Medical School. McGill was a very good school, and it was there that I first found out that there could be a rational approach to drug treatment of psychiatric disorders. Professor Heinz Lehmann was a gem of a

teacher. He could bring a patient into the room with a group of about fifteen of us. He would introduce the patient, and he would tell us to examine him/her. We were to watch the patient's behavior and discussed later what we saw. I can still remember, vividly, after over fifty years, many of the patients. To show us mania, in 1953, before drug treatment had been introduced, Heinz Lehmann brought in a female patient for us to examine. She was unable to remain still. She danced around the room, flitting from one student to the next saying, "Oh, what a beautiful tie you have! Oh, my, look at your jacket! It's gorgeous.....Your shoes are so polished," and she would go around to each one of us. We were all laughing with her, not at her. We enjoyed her presence. When she left, Dr. Lehmann said, "This is mania. This is a pure manic patient. You feel happy with the patient, you will enjoy the patient." Of course, when she did what she was doing in the class, for twenty-four hours a day, it was to become anything but enjoyable to her husband. But, nevertheless, this is the feeling of what mania induces. Another time he brought in someone who was depressed. The patient told us that he committed the unpardonable sin and we all felt the depression the patient experienced. The hebephrenic schizophrenic patient that he showed us, had received a PhD at McGill in biochemistry, before he got sick. One day, he was found wandering around in the nude on the mountain behind McGill. When he entered the room, he was telling us, "Ah, ha, what a wonderful idea, what a happy, happy day." He spoke nonsense with a high tone, although he was a big guy and we expected he would have a deep voice. Professor Lehmann explained that this was typical of hebephrenic schizophrenia. The patient is silly. Unlike the manic patient, you find the patient uncomfortably laughable. Another time he brought in a person, who came in well dressed with a tie, jacket with the daily newspaper under his arm. He sat down comfortably and when we interviewed him, we found absolutely nothing wrong with him. He was oriented in time and place. He knew current events. He seemed aware of everything. We finally asked the patient why he was in the hospital. Then, he explained, "Well, you know, these people don't understand me. My wife had this X-ray machine, and she was looking into my brain and telling me things to do. It became impossible, and because of that, I just had to kill her." Dr. Lehmann said, "This is an example of the island of abnormality in the mind of the paranoid schizophrenic." He warned us, "Don't turn your back on a paranoid schizophrenic. You'll have a nice conversation with him, and suddenly, he'll pick up the ash tray and hit you over the head with it." Well, this was Heinz Lehmann. Only he could carry this off. I don't know where he

found these typical patients. I've never seen them again. The patients that I encountered always had mixed, unclear diagnoses but he had these pure, probably rare, but typical patients in a large patient population at Verdun Protestant Hospital, which was the McGill teaching hospital for psychiatry at that time. There was another psychiatric hospital that was closer to the Medical School, the Allan Memorial Institute, which was up on the hill. There, I saw shock treatments given to schizophrenics, but we never really got the same feel for the disease that Heinz Lehmann was able to impart to us.

TB: What did you do after your graduation from McGill?

IK: Well, after I graduated from McGill, I took my internship and residency at Boston City Hospital. At that time, in the U.S., there was the "Berry Plan." Under this Plan, if you had enlisted in the Army during Medical School, they allowed you to take your residency, and then, you went into the Army only after you completed your training. Entry into the Army was postponed. But, I went to McGill, which was in Canada, and being out of the country, I had not been part of the Berry Plan. My draft board wrote to me in March 1957, that I would be drafted into the Army unless I enlisted by July 1. So I decided, I would enlist but would finish my internship and my second year of residency first, and then go into the Army. But the Army told me that I could not enlist until September. At that time, I had a wife and two children, having gotten married at the end of first year in medical school. I was very lucky to have a supportive wife. Our first child was born in Montreal during my last year of medical school and the second child was born during my internship in Boston. We had these two babies and I couldn't afford not to have a job for three months. So, I decided I would call the Navy, but the Navy gave me the same story, as did the Air Force. Then, I heard about the U.S. Public Health Service. They were accepting enlistments on the 30th of June. So, I decided I would apply. And I was accepted. I received a letter saying that I was assigned to the Tuberculosis Research Section because of my "background in mathematics." I had been a good mathematician in college. I won a prize at CCNY (College of the City of New York) for "Pure and Applied Calculus" and when I graduated from McGill, I had won the Hiram Mills Gold Medal in Biological Science along with Honors in Biochemistry. I thought that they had assigned me to a real research project. But I soon found out that this assignment was all statistics. At that time, I was caring for patients and I didn't want to lose this touch. I went down to Washington and explained, "I'm delighted that I'm with the U.S. Public Health Service;

however, I would like to be in a hospital where I see patients.” The personnel department was very accommodating, “Well, there are two jobs that are open in this new hospital on the outskirts of town, called Bethesda, and there’s a new clinical center.” I’d been at the old Boston City Hospital and when I walked into the beautiful new marble hallway of the Clinical Center at the NIH I thought, “I would take a job sweeping floors here.” It was a gorgeous place. I was interviewed by two groups of people. One group was in the Dental Institute. They were studying dental agenesis in patients with albinism. The other was a study of schizophrenics at NIMH. At NIMH, they wanted a physician to take care of the normal controls and a very select group of schizophrenics. That job was in the Clinical Center, whereas the other involved living in a trailer in a south portion of Maryland. It was in June and it was very hot. The trailer had no air conditioning, so the choice was an easy one, “I’ll be in the Clinical Center.” And so, by this accident, I chose to work with the project on schizophrenia.

TB: What was your task in the project?

IK: My first task was to go out to the mental hospitals and examine all of the patients that have been selected, to determine whether they are appropriate for admission for the schizophrenia project. Seymour Kety helped in designing this project. He wanted to find out whether or not there was a familial tendency towards schizophrenia and whether there was a biological difference between those schizophrenics that had a strong family history of schizophrenia and those that didn’t. My job was to make sure that the schizophrenics were healthy, except for their psychiatric disorder. So, I went out to the hospitals and examined them and made sure they didn’t have any Parkinsonian symptoms from their drugs, liver disease, etc. We brought into NIH fourteen schizophrenic patients; seven of them had a family history of schizophrenia. Some families were loaded with the illness with one parent, an uncle, a cousin, three or four people in the family blatantly schizophrenic. The others had absolutely no history of schizophrenia. Four hundred man-hours went into the examination of the history of these patients to select them. And so, we brought into NIH, seven that had the strong family history and seven that had absolutely no family history of schizophrenia. Since the schizophrenics didn’t complain about their illnesses, I didn’t have very much to do. It took about three months to select the patients, but after that I would go on ward rounds, which took about fifteen minutes in the morning, and I had free time all day. At that time, serotonin had just been found in brain. So, I wanted to find out whether or not serotonin

had anything to do with any brain function related to schizophrenia. I went to Marion Keyes, who was then head of the Section on Biochemistry in Seymour Kety's laboratory, and I told her I wanted to look in spinal fluid for 5hydroxy-indole-acetic acid, 5-HIAA, the metabolite of serotonin in the cerebrospinal fluid. Paper chromatography was at the time the most modern method for detecting such a substance and I proposed looking for 5-HIAA in spinal fluid using paper chromatography. To do this, Dr. Keyes told me, I had to get rid of the salts first and then do paper chromatography to find out whether or not 5-HIAA could be found. She also told me, "I'm writing a book, now, on allergic encephalomyelitis, and I'm not using my bench. Feel free to use my bench." I then went to the library to find out how to remove the salts from spinal fluid and made a large desalting apparatus with mercury bubbling up. It was one of those complex glass things; it reminded me of a cartoon I once saw, where cleaning ladies are cleaning the laboratory and inspecting a huge complex big glass apparatus with a boiling solution. One cleaning lady says to the other, "I don't know what they use it for, but I use it for making coffee." Well, that's what this thing looked like, but it worked. I was able to get the desalting apparatus to work and I was doing, anyway, lumbar punctures on the schizophrenic patients when they first came in, to be sure that they didn't have syphilis, etc. I had frozen some of the spinal fluid and decided I would try to detect the 5-HIAA in the CSF.

TB: Are we in the late 1950s?

IK: This was in 1957, shortly after serotonin was discovered in brain by Park Shore. About the same time, in 1957, it was decided to have a conference on catecholamines at NIH. The reason was that catecholamines had become very important. Ulf von Euler had, in the early 1950's, discovered that norepinephrine was the neurotransmitter of the sympathetic nervous system and a great deal of research followed his discovery seeking the role of catecholamines in disease states. Also, there was a hypothesis that adrenochrome, derived from the oxidation of epinephrine, might cause schizophrenia. The adrenochrome hypothesis was based on anecdotes that during World War II, when outdated adrenaline, which had become pink by the formation of adrenochrome, was used in England, people who got the injections with the pink adrenaline became psychotic. The hypothesis that catecholamines might be involved in causing schizophrenia was sufficiently important that it had to be investigated. Seymour Kety, who was Chief of the Laboratory of Clinical Science at that time, had spawned interest in biological factors in mental disorders. He is

regarded by many of us, as the father of Biological Psychiatry. We were encouraged to investigate various aspects of biological factors related to brain function and psychiatry. Kety encouraged Julie Axelrod to follow his interests in catecholamine metabolism and I was encouraged to examine tryptophan and serotonin metabolism.

At that time, Zeller had described that after giving a tryptophan load orally to schizophrenics and normal subjects, the increase in the urinary concentration of 5-HIAA was significantly lower in schizophrenic patients than in normal volunteers. Seymour suggested that, perhaps, since I was involved in measuring 5-HIAA anyway, I should look at this problem. So we loaded the patients and controls with tryptophan and collected their urines. Well, schizophrenics aren't very cooperative and the conscientious nurses would follow the schizophrenics around the ward to make sure that they got a complete urine collection. To encourage them to urinate, they were urged to drink a lot of water. As a result, the concentration of 5-HIAA in the two to three liters of urine that was collected from schizophrenics was low compared to that in the one liter of urine that came from the normal controls. Zeller had reported concentrations and not the absolute amount. Well, his findings of lower concentrations were confirmed; we obtained the same results that he reported. Yet, although the concentrations were low, the total amount of HIAA that was excreted was the same by the schizophrenic subjects as by normal subjects.

Also, about that time, Julie Axelrod had become deeply involved in the study of O-methylation as the route of epinephrine metabolism. This was an interesting story, because Julie, who was an expert biochemical pharmacologist, and had for many years worked with Bernard Brodie, just recently obtained his Ph.D, but was already a Section Chief in Kety's Laboratory. Julie attended the Federation meetings, in 1957, held in Atlantic City, where Armstrong described vanillylmandelic acid, VMA, in the urine, as a product of epinephrine in patients with pheochromocytoma. Since, on the basis of earlier experiments with ^{14}C -labelled epinephrine reported by Schayer, it was generally believed at the time that epinephrine was deaminated, Armstrong proposed that epinephrine was deaminated and then O-methylated to form VMA. But Julie thought this might not be the order of events and had the novel idea that maybe Omethylation was first, and more important than deamination. It was fortunate that Julie's laboratory was just down the hall from Julio Cantoni's lab. Cantoni had previously discovered S-adenosylmethionine (SAME), the methyl donor for such methylation. So, Julie got some S-

adenosylmethionine from Cantoni's lab, used it to incubate epinephrine with a homogenate of liver, and found a new spot on chromatography. But he could not prove that this spot was due to O-methylated epinephrine. It stained like a phenol and it seemed, by its extraction properties, to be an amine, but to prove that it's an O-methylated product, he had to have the authentic compound. Julie phoned Bernardt Witkop, who was head of the Laboratory of Chemistry at another institute, NIDDK, and asked if he could synthesize the hypothetical O-methylated product of epinephrine. The Visiting Scientist Program at NIH was just initiated, and Bernardt assigned the task to Shiro Sanoh, the first Japanese Visiting Scientist to come to NIH. Shiro synthesized metanephrine for Julie in three days, and by chromatography, they showed that it had the same retention, R_f value, and had the same staining characteristics as the substance formed from epinephrine and SAME in the liver homogenate. They published this in *Science*. Julie showed that formation of metanephrine was important; but he could not find any adrenochrome formation from adrenaline in animals.

Kety organized a group of us to present reviews in a symposium on newly emerging findings in biological psychiatry. Lou Sokoloff, Seymour Kety, Julie Axelrod, Elwood LaBrosse, and I presented summaries about various biological aspects of mental disease, and also about some of the pitfalls of studies in biological research in psychiatry. Much of this was about the mistakes that had been made. An example of these mistakes was the one based on the use of paper chromatography, a popular technique at the time. Based on urine samples from patients and from normal subjects, which were subjected to chromatography, there were reports of a spot that always showed up in urine from schizophrenics but didn't appear in the urine of the normal subjects. LaBrosse was studying schizophrenics, at the time; and he had normal controls, most of whom were volunteer Mennonites. These normal Mennonite men came to NIH to be volunteers in medical research instead of serving in the armed forces because they didn't believe in violence or war. Kety had arranged to have fourteen schizophrenics and fourteen normal controls in the study. All of the normal subjects were Mennonites, except one, and he was a little bit peculiar. When their urine was compared to that of the schizophrenics, there was a clear difference in the samples. The urine of all of the schizophrenics, except one, who had no family history of schizophrenia and who was a little bit different than the others, produced a specific spot on chromatography. Only one of the normal subjects had the spot, and he was not a Mennonite. He was also an older fellow,

a little bit different from the other control subjects. After searching to find out the nature of the spot, the “schizophrenia spot” in the urine, they found that it was caffeic acid, a constituent of coffee. The young Mennonites didn’t drink coffee and they didn’t smoke, but the older fellow, who was a little different, drank coffee. All the schizophrenics drank coffee, lots of it, but the one patient who was a little bit different, stayed away from coffee. So, it was the “coffee spot” that was different. Elwood LaBrosse was the person who was responsible for this work. This was a good example of the errors and pitfalls that were being made in schizophrenia research in early years.

Another important development was the introduction of reserpine, which was initiated by a pharmacologist from India, who went to various drug companies with the evidence that a folk medicine, Rauwolfia alkaloid, calmed animals and also excited patients. Finally, Ciba picked it up and isolated reserpine, which turned out to be a useful drug and was brought to market. Park Shore, in Brodie’s laboratory, showed that reserpine depletes brain serotonin and noradrenaline. When reserpine came into use to treat hypertension, it was found that it sometimes caused depression. The hypothesis that depression was related to the depletion of brain norepinephrine was partially based on this finding.

Julie Axelrod had been working with catecholamine metabolism and disposition in those years. He used to sit in an open laboratory. His desk was in the laboratory with a sink right next to the seating area and his workbench next to that, with a blackboard behind his desk. On that blackboard, he had written all of the questions, all of the formulas, and all of the outlines of the experiments that were being planned.

Seymour Kety had introduced radioactive adrenaline and noradrenaline into the laboratory. Seymour made an arrangement with New England Nuclear Company to make radioactive noradrenaline, so that we could follow it through the body. He did this for clinical purposes. Julie used it for the basic purpose to study the metabolism and disposition of these amines. I remember the time when George Hertting, a pharmacologist from Vienna, came to the NIH, and Julie and I were standing around discussing some findings. Julie said, “You know, after we inject ^3H -adrenaline intravenously into animals, we find that half of it is retained in the tissue.” He had done this research in intact animals in the mouse, and in cats. A large fraction of ^3H -adrenaline remained in the heart and Julie said, “It seems that adrenaline goes to where noradrenaline is and maybe

there's something special about this. Maybe uptake is important in some way." George Hertting, listening to the conversation recalled that after denervation, i.e., after cutting sympathetic nerves, nerves degenerate and the tissue becomes supersensitive to adrenaline. So, he said, "If the nerves are the place where the ^3H -adrenaline remains, that won't happen on the side where the nerves degenerate." Hence, George and I removed the right superior cervical ganglion from cats and waited for a week for the nerves to degenerate. We then injected ^3H noradrenaline and an hour later removed the tissues from the nictitating membranes and the salivary glands, from both sides. We found that the tissues on the side on which the superior cervical ganglion had been removed didn't take up the ^3H -noradrenaline whereas the tissues on the intact side did. The basis of supersensitivity became apparent. Since there was no uptake on the side where the superior cervical ganglion was removed, the uptake was perceived as a mechanism for inactivation.

At that time, there was a disagreement about whether O-methylation or deamination was the important mechanism for inactivation of noradrenaline. A Belgian pharmacologist, Zacq, had found that pyrogallol, a catechol, slightly potentiated the actions of adrenaline, whereas inhibition of monoamine oxidase had almost no effect. Of course, we now know that it is uptake that is the mechanism of inactivation of catecholamines released from the nerves. But, the fate of injected adrenaline is somewhat different. The question was whether O-methylation or deamination was important? I had suggested using radioactive labeling, by using double labeling, to find this out. It required the labeling of metanephrine with ^{14}C , which we could make with radioactive S-adenosylmethionine. We used this ^{14}C -metanephrine simultaneously with tritiated adrenaline. I did the experiment in patients, and together with Julie, I started to study the metabolism of catecholamines in rats. From the ratio of tritium to carbon in the urinary metanephrine, it became clear that O-methylation was the predominant route of metabolism of the administered catecholamine in rats and in humans. Yet, inhibition of O-methylation didn't potentiate the effects of nerve stimulation. George and Julie showed that cocaine, which was known to potentiate the effects of sympathetic nerve stimulation, prevented the accumulation of injected ^3H -noradrenaline in tissues. The concept that neuronal reuptake is important for the inactivation of a neurotransmitter stemmed from that early work, done around 1959, and published in 1960 and 1961.

During the studies of urinary ^3H -catecholamine metabolites, a new metabolite had appeared in the urine of rats. It was neither VMA nor metanephrine. The metabolite could not be obtained from N- ^{14}C -labeled metanephrine but did form after administration of the side chain labeled ^3H -catecholamines. It turned out to be 3-hydroxy-4-hydroxyphenylglycol (MHPG). In rats, MHPG was the major urinary catecholamine metabolite. In humans, MHPG is also excreted in urine, but VMA is the major urinary metabolite. At that time, we thought that this was a species difference in the metabolism of the intermediate aldehyde metabolite, but this was not the case.

TB: What year was MHPG identified?

IK: In 1960. In July 1960, I went off to complete my residency in internal medicine and returned to NIH after one year. Seymour Kety had left NIH, by then, to become Chairman of the Department of Psychiatry at Hopkins. Seymour invited me to go to Hopkins with a joint appointment in the Departments of Medicine and Psychiatry, but in order to “pay back” NIH for the period of time that they allowed me to take my residency, I had to remain at NIH for at least one more year. While I continued doing research on noradrenaline, another compound, melatonin, became of interest.

Melatonin, which is 5-methoxy-N-acetyl serotonin, was discovered by Aaron Lerner at Yale. He presented a seminar on melatonin at NIH and suggested that the substance was metabolized to 5HIAA. Lerner thought that after the N-acetyl and the methyl groups are removed from melatonin, the resulting serotonin is converted to 5-HIAA, a metabolite of serotonin. I had been working with double labels at the time and suggested to Julie that we label the whole molecule of melatonin. We labeled the O-methyl group with carbon and the acetyl group with tritium. If Lerner was right, we should not find any radioactive compounds related to indoles in the urine. If we would find radioactive compounds related to indoles, we had the capability to determine whether one or both ends of the administered melatonin remained intact. Michael Pare, a psychiatrist from England, joined us at that time and participated in this project. Well, it turned out that the ratio of carbon (that labeled the O-methyl group), and tritium (that labeled the acetyl group) was identical in the urine to the ratio in the melatonin that was injected. Clearly, there was no deamination or deacetylation. When we gave large amounts of unlabeled melatonin, paper chromatography of the urine sprayed with Ehrlich’s reagent, which stains indoles, showed a sky blue spot. We found that the same type of spot was present in the urine of a woman that Aaron

Lerner sent us, who had been given large doses of melatonin to treat her melanoma. Of course, it didn't help melanoma, but we had the urine and she had this sky blue spot, also. Well, I didn't know much about that type of chemistry, but NIH is a wonderful place, because there's an expert in almost any field there. Among them, was an expert in the field of indoles, Evan Horning. I took the material to him, and he recognized, from the sky-blue color reaction with Ehrlich's reagent, that it was a 6-hydroxy-indole. Thus, 6-hydroxymelatonin, and 6hydroxymelatonin sulphate were found to be the major metabolites of melatonin.

It was about this time, that Dick Wurtman joined the laboratory. There were also a number other young scientists coming in from all over the world. George Hertting had already been there. Leslie Iversen and Jacques Glowinsky came to the NIH to work in our lab, in Julie's lab, and these people became the founders of a major portion of the biochemical aspects of pharmacology, particularly in the nervous system. So, many of the stars in neuropharmacology, particularly in the amine area, grew up in the laboratory that was established by Seymour Kety. Seymour, after one year at Hopkins, decided that Hopkins was not for him. He told a story, that when he first went to his new office at Hopkins and sat down in the chair of the department, the chair broke. He claimed that he felt this was an indication that he might not last. After a year, he decided to return to NIH. And, when he came back to NIH, he told me that I should stay. He wanted me not to go to Hopkins. And I agreed to stay. At that time, I had the good fortune of being able to hire a wonderful technician. Edna Gordon was a woman who had worked with Jarvis on phenylketonuria in New York. After she had gotten married, had a child, she left work for about eight or ten years. But at this point in time she was ready to return to the laboratory. When I went home and I told my wife, Rita, about this woman whom I had interviewed, she said, "You should hire her, because that's the type of person that would have gone on to get a Ph.D." And she was right. Edna Gordon was a gem. She did all of the work that I couldn't do with the precision that she brought. She taught me how to keep notebooks. She kept all of the data, beautifully organized. Also, a normal volunteer, Dale Horst, a Mennonite, had started to work in the laboratory. Dale was bored on the ward on which he worked and offered to help out in the lab. After a while, Dale decided that he had some interest in biology. He left NIH, went back to school and majored in biology. After receiving his degree he applied to NIH, looking for a position as a technician. I gave him a job in the laboratory. As part of the research that I was doing, I had learned how to inject the tail vein of

mice and rats to get urine flowing so we could get clean samples. I asked Dale to try to learn how to do this and explained it to him that it will not be easy to do it initially, that it would take time to get the hang of it, and that he must be very patient. After explaining all of this to him, and also how to put the needle in underneath the skin in the tail of the animal in an area where the vein can be seen, using a yellow light, preferably, he easily did it the first time he tried. He had done it beautifully; much better than I would have done it. He then constructed a rack, so that we had eighteen animals set up with intravenous infusions of fluid going in their vein while their urine was collected. It seemed as if the fluid input were connected to the penis; because as fast as the fluid was infused, the rats began to urinate at almost the same rate. We were able to get half-hour urine samples from these animals and could study the kinetics of the excretion of metabolites of the labeled catecholamines injected. We started to study the effects of drugs on the excretion of the products of ^3H catecholamines. We could distinguish which were the immediate metabolites in the urine excreted in the first hour. They were mostly O-methylated. After several hours, however, the major metabolites were found to be deaminated metabolites. After tyramine was administered, there was a large increase in sympathetic responses, and the urine contained increased amounts of O-methylated products. But after reserpine administration, that depleted catecholamines from their stores, and interfered with sympathetic function, we found marked increases in the deaminated metabolites in the urine. That led us to the conclusion that the reserpine-induced depletion of amines is accomplished by interference with their storage. If the catecholamine is released into an active form outside the nerve it is O-methylated. But O-methylation is relatively unimportant for inactivation of most of the released amines, because most of the amines are inactivated by reuptake.

TB: When did you become a section chief at NIH?

IK: By 1963, I had become a Section Chief. There were a series of outstanding postdoctoral fellows who came to work with Julie Axelrod and me during the next decade. I already mentioned Leslie Iversen, Jacques Glowinski and Dick Wurtman by name. Others included Ross Baldessarini, Sol Snyder, Dick Wurtman, Jose Mussachio, Joe Fischer, Saul Schanberg, Joe Schildkraut, Goran Sedvall, Lou Lemberger, Tom Chase, George Breese, Richard Kvetansky, Perry Molinoff, Dick Weinshilboum, who later made their mark as outstanding investigators and leaders in academia and in the pharmaceutical industry.

This was the time of the Korean War and there was a draft to serve in the military. Those who joined the US Public Health Service could satisfy their military obligation by serving at NIH, rather than go to Korea. This was a popular option, and in one year, I had six young physicians, each of whom were first in their class in medical school, apply to come to our Laboratory as a Research Associate. They would serve for two years and we really had star applicants. One of them was Joe Schildkraut, a young psychiatrist who joined me, in 1966, after having extensive discussions with Seymour Kety. Together, building on the earlier observation that reserpine sometimes induced depression, they gathered together the evidence that supported the hypothesis that catecholamine depletion was the basis of depression. Goran Sedvall, another psychiatrist who joined our laboratory, subsequently became Chair of the Department of Psychiatry at the Karolinska Institute. Joe Schildkraut, of course, became a professor of psychiatry in Boston. Ross Baldessarini, then a young medical student at Hopkins, was referred to our lab by Dr. Kety who phoned me, saying, "This fellow is very bright. Why don't you take him as a summer student?" At that time, we were interested in S-adenosyl methionine and we were employing the double label technique again, using melatonin as the product. Melatonin could be separated from both the added ^{14}C -methyl-labeled S-adenosyl methionine and from ^3H -N-acetyl serotonin. The added ^{14}C -methyl-labeled S-adenosyl methionine was diluted by the tissue S-adenosyl methionine and enzymatically converted to melatonin. From the ratio of the carbon to tritium, we could calculate how much endogenous S-adenosyl methionine had been in the tissue. This was the project that Ross did over the summer of 1963, and we published it first as an assay for Sadenosyl methionine. Several years later, Ross came back to our laboratory as a Research Associate. Seymour Kety, by that time, as I said it before, returned to NIH and I had become a Section Chief. Catecholamines had become important, not only in psychiatry, but of course, to all those who studied the sympathetic nervous system. Hence, future neurologists, anesthesiologists, and internists, came through our laboratory at one time or another. Mike Roizen, who became Chairman of the Department of Anesthesiology at the University of Chicago, had his first experience with catecholamines in our Laboratory. In the late 60's, we started to study the release of noradrenaline and related compounds from the sympathetic nerve endings. Joe Fischer, a surgeon, while in our Laboratory, became expert at perfusing cat spleens with intact sympathetic nerves. This was a very useful means of studying amine release when nerves were stimulated. The people that came to our

laboratory and left, who have had a major impact in developments in the drug industry as well as in academia include Perry Molinoff, Steve Paul, Gus Watanabe, and Bill Potter. Because of the responses of the sympathetic nervous system in emergencies, we became interested in stress, also. Stress, of course, elicits responses of the sympathetic nervous system and the adrenal medulla. Richard Kvetnansky, who was from Bratislava, came as a visiting scientist, and, brought with him a model for studying “immobilization stress” in rats that he’d been working with in Bratislava. But in Bratislava, they didn’t have the techniques that we had to examine catecholamines. We started to study the effects of stress on the adrenal medulla and on the sympathetic nervous system, and particularly enzyme induction. Goran Sedvall had developed a technique for stimulating, in a rat, the sympathetic nerves on one side of the head, on the sympathetic chain in the neck, and we could compare the changes in the two sides. Using double label techniques, giving DOPA labeled with one isotope and tyrosine labeled with a different isotope, he was able to show that the conversion of tyrosine to DOPA was the rate-limiting step in norepinephrine synthesis and that it was this conversion that was enhanced by nerve stimulation. DOPA was easily converted to noradrenaline, but if you stimulated the nerve, more tyrosine was converted to noradrenaline; so the carbon/tritium ratio in the salivary gland was increased on the side where the nerve had been stimulated. This was the first indication that sympathetic nerve stimulation increases tyrosine hydroxylase activity. We subsequently found that DHPG (Di-Hydroxy-Phenylethylene-Glycol) is the major initial metabolite of noradrenaline and is converted by O-methylation to MHPG in the tissues. The MHPG enters the blood stream and is converted in the liver to VMA, which is the product that is excreted and can be measured in the urine in humans. We could then use blood levels of MHPG as a basis for studying sympathetic activity in humans, and we used the measuring of MHPG blood levels in many studies. Graham Eisenhofer, Dave Goldstein and I continued to develop much of the MHPG story.

TB: Are we now in the mid 1960's?

IK: Well, we’re spanning the mid ‘60's; we conducted a series of studies on false transmitters in the early 1970s. The concept of false transmitters began with the introduction of α -methyldopa. When α -methyldopa was given, α -methylnoradrenaline was formed and largely replaced norepinephrine. α -Methyldopa is used as an anti-hypertensive agent, because the α -methylnoradrenaline formed doesn’t stimulate the α -receptor and norepinephrine is more active at

β -receptors, which causes vasodilation. In the brain, after α -methyldopa administration, α -methyldopamine and α -methylnorepinephrine are formed.

TB: You have made major contributions in setting the neuroscience foundation of neuropsychopharmacology. Am I correct that you were the recipient twice of the prestigious Anna Monica Award?

IK: Yes, once with Joe Schildkraut, and once, alone, for the MHPG story. Joe led a group of us that won the first Anna Monica Award for the work that led to the concept of noradrenaline as being involved in depression. Later on, when the MHPG story developed, this was almost ten years later, I won the Anna Monica Award for the MHPG story. Our research clarified the important role that MHPG plays as an index of sympathetic activity, and as a means, for using plasma MHPG and CSF-MHPG to evaluate norepinephrine metabolism in brain. Many people contributed to these studies, and I was lucky to have been singled out for the award. At the time, MHPG was a central area of our research.

TB: Tell us about some of the other young people you didn't mention, as yet, who spent time in your laboratory.

IK: We had a number of young physicians, who began their research careers in our laboratory. One of them, Steve Silberstein, joined us to study tissue cultures. He's currently a neurologist and is studying headache. Another one was Justin Zivin, who was doing research with us on stroke and trauma and had been promulgating the idea that catecholamines have an important role in the development of the pathological changes after spinal cord injury. People like Silberstein and Zivin got their early training with us, and then, they branched off into their own respective areas of research. It's given me great pleasure to see how they developed and continued to do research, not necessarily in our field, but using the conceptual framework they learned in our Laboratory in their investigations, or in Walter Cannon's words, "the way of an investigator." I learned from Julie and from Seymour how to think and how to manage a laboratory, and I see that the things that I learned I've been able to pass on to them, like to my children.

TB: Isn't your son a molecular biologist?

IK: My son started as a gastroenterologist but has evolved into a molecular biologist as well. As part of the requirement to participate in research to obtain his Boards in gastroenterology, he learned to clone a gene. He was new to this area of research, but became quite good at it, and I

learn a good deal about molecular genetics from him! We live now in a new world of research and I've had the good fortune of bridging the time when we knew little about the molecule, and current times, when we know so much about it. In this new world, information comes faster than we can possibly digest it. We need computers to keep track of everything that's going on, and it's difficult to see how we managed at the time, before 1965, when we didn't have Medline. In the 1980's, you would have to have gray hairs to remember what happened before Medline, and this is the time I bridged.

TB: Weren't you involved in the 1-Methyl-4-Phenyl-1,2,3,6-TetrahydroPyridine (MPTP) story?

IK: There was a turning point in my research in the late 1970's. In 1978, I got a call from a neurologist, who said that he had a very peculiar type of patient, a twenty-four year old boy, who had been thought to suddenly develop catatonic schizophrenia. His mother found him in his room, lying in bed in his feces, unable to move, and took him to the local hospital. The boy grew up in the shadow of NIH, he was taken to the local Suburban Hospital where they postured his hands and after diagnosing his disorder as typical catatonic schizophrenia, they sent him off to a mental hospital. During the next month or two, he became more rigid and they called in a neurologist. The neurologist recognized that the boy appeared to have severe Parkinson's disease rather than catatonic schizophrenia. When he was treated with L-DOPA, lo and behold, he suddenly loosened up and said, "What have you guys been doing to me?" About four hours after he got the L-DOPA, he was back into his prior state. They had given him ammonia to smell, trying to get a response, but he was unable to move, as later he said, "I just couldn't carry out any actions." So, they had started to treat him with L-DOPA. So, the neurologist called me and asked if I was interested in studying this young man, and I said, "He sounds fascinating, yes, let's bring him into NIH." After he was admitted to NIH, Dr. Davis, a young NIMH psychiatrist on the ward, while exploring the patient's history, found out that the patient was abusing drugs for some time; and to increase the effectiveness of the drugs he was abusing, he started to take Demerol with cocaine. He felt that this was a marvelous mixture but had a great deal of difficulty in getting Demerol. He was a bright young man and went to the library where he found out that there were other compounds that were very much like Demerol that he could synthesize himself. So, he set up a laboratory in his basement to synthesize a derivative of an isomer of Demerol, in which the carbon and the oxygen atoms were reversed on the molecule. He had all the equipment for doing this, and when he tried the

compound he synthesized, he thought it was wonderful. He obtained the crystalline compound and was taking about twenty five milligrams of it, at a time. He decided, during one summer, that the amounts he was preparing were too small, and he tried to make a big batch. While preparing a big batch, he realized that he would lose a lot of the compound if he recrystallized it. So he didn't recrystallize it and took some of this material. After two doses, he suddenly developed the syndrome for which he was hospitalized. This was the first case of MPTP toxicity. Sandy Markey, who just about that time joined our laboratory to head the mass-spectroscopic facility, went to the patient's house to try to get some of the substance that the patient had made, but his mother had cleaned up his son's laboratory and threw out most of the stuff. The only thing left was one desiccator. That desiccator had a little bit of the powder left in it, that Sandy was able to analyze by mass-spectroscopy, and found it contained MPTP, along with two other compounds. We thought that we should publish this interesting case, but it was very difficult to get it into print. But finally, we did succeed. About a year or two after this, in California, there was an outbreak of Parkinsonism among drug addicts and Bill Langston traced down the compound that had been used and sent it to Sandy Markey, who found out that it was MPTP. At the time, we had tried this compound in rats, guinea pigs and rabbits, with little notable effect. However, it did cause a Parkinsonian syndrome in monkeys, and the MPTP story really started a new era in neurology. As you know, DOPA had been suggested as a potential treatment for parkinsonism after dopamine had been discovered by Carlsson in the late 1950's, and in the early 1960's, Hornykiewicz reported that dopamine was depleted in the brain of Parkinsonian patients. Early attempts at using DOPA in the treatment of patients with Parkinson's disease failed because of its side effects, but in the late 1960's, George Cotzias was brave enough to give the large doses of DOPA that were needed and proved the efficacy of DOPA in alleviating the symptoms of Parkinson's disease. Soon after, the side effects of DOPA, which were largely due to formation of dopamine outside of the brain, were found to be preventable by the use of peripheral DOPA decarboxylase inhibitors. Such peripheral dopa decarboxylase inhibitors were introduced. At the time, Gus Watanabe studied the effects of DOPA after the administration of peripheral decarboxylase inhibitors on the vascular system. Gus later became vice president of Eli Lilly. Tom Chase was also with us as a Fellow, in those years. He had been studying the release of compounds from brain slices with electrical stimulation. Later Tom was promoted to Section Chief at the Institute. Subsequently, he became scientific director

of the Neurology Institute. In 1983, I succeeded Tom as scientific director of the Neurology Institute.

TB: Any further developments in the MPTP story?

IK: At about the time, after the MPTP story had developed, and became increasingly well known, I received a telephone call from Denmark about a young chemist that had suddenly developed Parkinson's disease several years earlier. He had been working in the drug industry and had made a large batch of MPTP, which had been used as an intermediate in the synthesis and manufacture of some drugs. He had made several large batches of this chemical and after recrystallizing it, he spread it out on paper with his hands to dry it. Although he went home sick that day, he did the same thing a week later. He got sick again, but never returned to work, because he had developed severe Parkinsonism. I traveled to Denmark, and after confirming the diagnosis, I asked him to come to NIH. He agreed and we arranged for him to come to NIH along with Dr. Pakkenberg, his neurologist. At NIH, this brave patient agreed to be taken off his L-DOPA. Dr. Pakkenberg noted that, after discontinuation of medication, the patient's Parkinson's disease became aggravated. It became as severe as it was ten years earlier, at the time he was put on medication. Ten years of treatment with L-DOPA had not affected the severity of his Parkinson's disease. The patient was still responding to his medication after ten years of treatment, without developing dyskinesia that is often a problem after long term treatment of advanced Parkinsonism.

In a parallel development, Stan Burns, who had been studying the effects of MPTP in monkeys, developed the first animal model of Parkinson's disease. This was followed, a short while later by Kris Bankiewicz, with whom we were able to produce a hemiparkinsonian animal. We could make half the brain Parkinsonian by infusing MPTP in one carotid artery. The MPTP, delivered to only one side of the brain caused a Parkinsonian movement disorder on the opposite side of the body. Like rats that had received 6-hydroxydopamine into one side of the brain, the monkey circled towards the affected side. The monkeys had all the expected abnormalities of Parkinsonism but had it only just on one side. An affected animal would be able to reach for food with his hand on the opposite side. And he was very smart. If you offered him two pieces of food, he wouldn't reach with two hands. He would take the first piece and put it in his mouth, and then, reach for the second piece with the unaffected hand, whereas before being treated with MPTP, they would always reach with both hands. It was clear that he wasn't able to use the hand on the

affected side. After L-DOPA treatment, the monkey was able to reach for the food with both hands. We could measure the circling effect, as it had been done in rodents made hemiParkinsonian with the administration of 6-hydroxydopamine for studying dopaminergic systems. The MPTP treated hemiParkinsonian monkey became a useful tool for studying treatments of Parkinsonism. Kris moved on to study the effects of fetal tissue implants, but US government policy prevented NIH scientists from using fetal human tissue implants. In fact, they frowned on use of fetal tissue in research of any type at that time. Private funds allowed such research outside of NIH. Later, the same animal model of Parkinson's disease was used to study the effects of transfer genes into the brain of animals, whether it be rats or monkeys.

We continued to study stress in our laboratory, another area of research we conducted that has been highly productive. The sympathetic nervous system, of course, controls blood pressure. In our early studies of patients with orthostatic hypotension, many years ago, Mike Ziegler and I found that patients with orthostatic hypotension could be divided into two groups. One group of patients had central nervous system disease, with their sympathetic nervous system essentially intact. They had normal plasma catecholamines at rest, but when they stood up they didn't have the normal elevation of plasma catecholamines. These patients had multiple system atrophy in their brain. In the other group of patients, central nervous system was intact, but the sympathetic nerves were almost absent. This group had peripheral autonomic neuropathy, with absolutely no symptoms of central nervous system disease. Their orthostatic hypotension was associated with abnormally low plasma catecholamines, as well as a failure to increase the plasma catecholamine levels when standing. These patients have a better prognosis because only their sympathetic nervous system has failed.

We had been studying false transmitters and one of the early false transmitters that interested us was labeled with fluorine, fluorodopamine. I anticipated that it would be useful for imaging the sympathetic nervous system. If fluorodopamine is injected intravenously, it is taken up into sympathetic nerves, where it can be converted to fluoronorepinephrine. I thought that if ^{18}F labeled fluorodopamine is used, we could detect it in the sympathetic nervous system in the periphery and determine its distribution by PET scanning. We saw some patients with Parkinson's disease who developed orthostatic hypotension that was attributed to the accumulation of dopamine instead of noradrenaline in their sympathetic nerves after being given high doses of L-

DOPA. Dave Goldstein showed that these patients had degeneration of their peripheral sympathetic nerves, which could be demonstrated using ^{18}F -fluorodopamine and PET scanning of the heart. It was a new observation that we published in the *New England Journal of Medicine*. Later, the observation was amply confirmed. Dave Goldstein was doing the PET studies in humans; it took him about ten years to develop his method from the time that we used fluorodopamine accumulation in tissues to label noradrenergic nerves in animals. The work to develop the method began with “Mike” Chiueh, with unlabeled fluorodopamine. Graham Eisenhofer followed it up using ^{18}F -fluorodopamine made from the excess of ^{18}F -fluoro-dopa that was being prepared for imaging dopaminergic neurons in the brain. We did the same experiment that we had done many years before, using unilateral sympathetic denervation. In a dog, we removed the superior cervical ganglion on one side, gave ^{18}F -fluoro-dopamine, and used PET imaging to examine the effects on the accumulation and retention of the ^{18}F fluorodopamine. We found that the denervated side didn’t have any radioactivity, whereas the salivary gland on the intact innervated side did. We repeated this experiment in humans and found that we could not visualize with ^{18}F -fluoro-dopamine sympathetic nerves in the hearts of patients with orthostatic hypotension who had been diagnosed as having primary autonomic failure. The other group of patients with orthostatic hypotension, who were clinically determined to be suffering from multiple system atrophy, appeared to have intact cardiac sympathetic innervation. Although they had normal cardiac sympathetic innervation, they couldn’t appropriately activate their sympathetic nervous system because of their central nervous system disorder. These patients sometimes have Parkinsonian symptoms. So it appeared that we have a spectrum of patients who display some Parkinsonian features with orthostatic hypotension as their primary symptoms. Many patients with Parkinson’s disease have orthostatic hypotension. Although originally it was thought that the orthostatic hypotension was secondary to L-DOPA, it has become evident that the orthostatic hypotension is due to the degeneration of the sympathetic nerves in the heart and probably, also, elsewhere. Both internists and neurologists were interested in orthostatic hypotension; so, several of them have come through the lab who’ve been interested in such studies. One of the first was Ron Polinsky, a neurologist, who has gone on to a career with drug companies. Another one was Dave Goldstein, who was to become a leading figure in this area of research. Over the years, I’ve been tremendously fortunate in having people with broad expertise to join our laboratory. They

benefited from the excitement about science that pervades the NIH. To repeat it again, Leslie Iversen, Jacques Glowinsky, Sol Snyder, Dick Wurtman, and Perry Molinoff all spent their early years in the Laboratory of Clinical Science with Kety, Axelrod and me. In psychiatry, Joe Coyle, Steve Bunney, his brother, Biff Bunney, Mike Ebert, Fred Goodwin, and Dennis Murphy, as well as others, began as young post-docs in our laboratory. Dick Weinshilboum, who went to the Mayo Clinic, started his work on the genetics of different enzymes with studies of S-catechol-O-methyltransferase in our laboratory. Dave Dunner, Walter Kaye, and Bill Potter also came through the lab. Martha Weinstock, who is chairman of Pharmacology at Hadassah, came to work with us as a visiting scientist. So did Giora Feuerstein, originally from Israel, who stayed here, in the pharmaceutical industry, Joe Fisher, who was a surgeon, and is now chairman of the Department of Surgery. He and Ross Baldessarini carried out studies of S-adenosylmethionine to try to explain some of the deficits in hepatic encephalopathy. Joe, as a surgeon, made portal vein shunts in animals, and then, studied the effects of this portal vein shunt on the methylating processes in brain. The people that have come through the NIH are a source of pride and we keep track of their progress and accomplishments. They're "family."

The NIH has been very good to me and it's given me a great deal of pleasure over the years to have worked and been taught by such stellar people. I'm grateful to the teaching of people like Heinz Lehmann, who, when I was a medical student at McGill, really introduced me to psychiatry, and of Seymour Kety and Julie Axelrod, my supervisors and collaborators, and of the many, many young post-docs that have come through our Laboratory. I also have benefited from several outstanding technicians, like Edna Gordon and Virginia Wise. These are people who spent thirty or forty years working with me and ensuring the quality of our studies. Edna Gordon, unfortunately, has died. Virginia Wise is retired. She lives near NIH, and I see her every once in a while, and some of my secretaries, who have retired, have been with me for twenty years. Virginia has visited scientists that had spent time at NIH, like George Hertting in Vienna. They have been friends for over forty years. There is a unique perspective of seeing the carryover from the old pharmacology to the new molecular genetics and to look ahead to see that molecular genetics is not going to be the total answer. It's going to raise more questions than we can answer and the pendulum is going to swing back towards the intact animal research, the polymorphisms, the genomics, the informatics that we have now. The future direction of the College is going to

be fun to follow. Many of the people that I've talked about are members of the ACNP; some are foreign corresponding members from abroad. There are also those who are in other professional organizations, such as in neurology, anesthesiology, internal medicine, and some others who are working in drug companies. All these people contributed immensely to the intellectual environment of NIH and have had a major impact on medicine, psychiatry, neurology and anesthesiology in the United States and abroad. It's been such a great pleasure to work with them, and the many, many friends that I've made at ACNP. I am a Past President of ACNP, so I keep going to the Past Presidents luncheons. I have also continued for many years as Treasurer.

TB: When did you become a member of ACNP?

IK: In 1968, Sid Udenfriend and Seymour Kety were the people that urged me to join this group. It was very fortunate for me that I did.

TB: When did you become president?

IK: In 1992. The theme that year was to put the "Neuro" back into Neuropsychopharmacology. As president, I tried to do that. It may have been premature, but I think that it is also the theme of the current president, Steve Paul. Steve is another Laboratory of Clinical Science (LCS) alumnus, as was his predecessor at Eli Lilly, Gus Watanabe.

TB: All of them were in the LCS?

IK: Yes, all of them. They've grown up. They are analogous to children and grandchildren, if you like. They have expanded beyond the areas that we've been studying, whether it was depression or Parkinson's disease or orthostatic hypotension. But there remains some overlap with the main theme being brain function, not only psychiatry, but for neurology, anesthesiology, internal medicine, etc. For example, Alzheimer's disease is being studied in many Institutes: by the Institute of Aging, by the Neurology Institute, by the NIMH. No one institute can lay claim that it's the only one to study the brain. The Child Health Institute has a tremendous influence on what's becoming neuroscience and neuroscience encompasses so many disciplines. This is being recognized more and more widely.

TB: You have been in research in neuroscience since 1950s, the time of paperchromatography and the discovery of monoamines in the brain.

IK: Yes, that is right. I've seen the field develop and it's been a real privilege to work with the people who had so much impact on the development of the field.

TB: Are you still involved in the training of young researchers?

IK: Yes, I'm still involved. I am officially retired, but I'm a Scientist Emeritus at NIH, so I have my office, and most importantly, parking space. Although I do not have a lab bench, I still have discussions with post-docs and I'm able to bounce ideas around or have people come to me and use me as a sort of memory. Having the gray hair, I am supposed to remember what happened a long time ago.

TB: Your bibliography reflects the development of neuropsychopharmacology.

IK: Well, partially, yes. I've published over seven hundred papers, and that's largely due to the people that worked in the lab. You know, I had these talented people that came through that really spark your interest and keep your enthusiasm going.

TB: But still, it was you who trained them.

IK: It's mutual. They trained me; I trained them. And, it was a mutual interaction. When they come to a new lab, they teach new ways of thinking. They raise problems and the solving of these problems is a joint effort. It's something that I like; to interact and draw out and be drawn out, but it's mutual. It's never a one-way street.

TB: It seems that your research had a great impact on psychiatry and you're not a psychiatrist.

IK: Well, I am not a psychiatrist. Neither was Seymour Kety. The Laboratory of Clinical Science, which he started and I inherited, trying to carry on the tradition, really was a founder of biological psychiatry based on what has now become the discipline of neuroscience. Kety's lab probably trained half of the people that were in on the beginning of biological psychiatry in this country. The people we trained, of course, continued to train others, and we're now on the second generation and third generation of people who are trained by them. But, it all really stems from Seymour, who got the Lasker Award for his lifetime contributions. He started out as a physiologist and developed the first method for measuring cerebral blood flow, for which he really became famous. Then Lou Sokoloff, who was initially really interested in psychiatry, and Seymour exchanged ideas, and, then changed their courses of research interest. Lou went on to become more of the physiologist and developed the deoxyglucose method that is now used for imaging brain blood flow with PET scanning, whereas Seymour picked up the psychiatry and carried the ball on that and developed biological psychiatry. He's really considered by many to be the father of biological psychiatry in this country.

TB: And it seems you have made, in addition to your research, a major contribution by training many of the people who became leaders in the field. It's a most important contribution

IK: The most important contributions were the people, the people that have come through the lab, and what they've done afterwards. It's been a pleasure and a source of great satisfaction to me. I've worked with melatonin, with MPTP, with false transmitters, with brain imaging, with heart imaging. All of these things are relatively minor compared to the people that have come through and have gone on to do research, both at the clinical level and at the basic level, and the impact they've had on the drug industry, on the thinking in the field, on the whole neuroscience, on neuropharmacology. That is what I consider to be my greatest source of satisfaction.

TB: You should feel very pleased with the results. Look at the changes that had taken place in the field, and not just in the United States.

IK: Yes, Marta Weinstock in Israel, Sedvall in Sweden, Glowinski in Paris, Hertting in Freyburg...They are all over the world. There's also Corsini, who is now in Pisa. Many of these people became heads of departments, and they send their young people to NIH. So we've had a number of people come from them. There must be over a hundred who've come through at various times and spent up to two or three years with us.

TB: During the years, have you been affiliated with any university?

IK: Just with local universities. I have an appointment as an Adjunct Professor at Georgetown and at the Armed Forces Medical School across the street from NIH, and of course, you know, I lectured at four minority colleges when I was president of the ACNP. I also had the good fortune to have attended many international meetings, and catecholamine conferences that have been held every few years to bring things up to date. I was at all the International Catecholamine Symposia that were held every few years throughout the world. Dave Goldstein was President of the one held in California, in 1996. It included a wide variety of interests, from very basic neuroscience to the clinical studies of cardiovascular disease, pain, neurologic disorders, psychiatry, and everything in between.

TB: Didn't the people who worked at the LCS, at a certain point in time, organize a gathering at one of these conferences and had a Festschrift in your honor?

IK: Yes, that was at the Eighth International Catecholamine Symposium at the Asilomar Conference Center. That was very nice. Many of my old post-docs contributed to the Festschrift

in my honor. It brought back old memories such as the work I did with Sophia Zukowska, who is professor now at Georgetown. She first came to our laboratory about 25 years ago. I first met her in Bratislava, at a meeting on Stress organized by Richard Kvetnansky. When she presented her work at the meeting, she expressed interest in coming to NIH. She came and stayed with us for three or four years. In fact, she and Dave Goldstein were the ones who did the work on monoamine uptake. When Dave came to me with an idea of trying to find out what the concentration of noradrenaline is at the synapse, he suggested the administration of tyramine. For a number of reasons that couldn't be done, but that started me thinking about how it could be done. We compared the effects on blood pressure of stimulating the spinal cord of a pithed rat with the effects of infused noradrenaline. This was done by comparing the pressor response curves to the plasma noradrenaline levels in relation to the blood pressure. We found that you have to raise catecholamines in plasma to much higher levels with exogenous norepinephrine than the levels in plasma attained with an equivalent pressor response elicited by stimulating the spinal sympathetic outflow. The reason for this is that there is uptake in between the plasma and the synapse. But the reuptake is the same, whether the norepinephrine is coming out or going in.

So the concentration that you obtain during stimulating the nerve is less than is at the synapse, but when you give it exogenously, the concentration in the blood is higher than at the synapse; the synaptic concentration is in between. So, by comparing the log of the plasma catecholamine blood pressure response curves, the concentration in the synapse is halfway between; the logarithmic mean of the concentrations at any given pressor level. To prove that this was the case, we gave desipramine and the curves moved closer together because the uptake was blocked. The exogenous catecholamine gets more effective, the less of the endogenous NE is removed, and the curves move together towards the synaptic concentration. But that's another story that has been applied clinically to study patients with orthostatic hypotension.

TB: Your research embraced a wide range of different areas. You were involved first with research in schizophrenia, or even before with research of making a mirror. That was probably crucial...

IK: It may well have been. I sometimes think my father was very wise in the way he stimulated me.

TB: And obviously, you are a dedicated teacher.

IK: You know, everything is taught earlier now than before. When my son went to high school, they also told him about how to test for aldehyde, by making a mirror, but there they told him to clean the glass. I guess I've told this story so often, that everybody now knows that you had to clean the glassware. So they told the whole class, you have to clean the glassware to get a good mirror and he brought home this test tube with the mirror. Of course, he was thrilled because he had reproduced what I had done at about his age.

TB: Is there anything we left out and you would like to add?

IK: No, I just think it's been such a privilege to be a member of this college, to be part of the NIH, and to have lived during this marvelous transition, and to see that in the future even greater contributions will be coming from molecular biology to provide a better understanding of brain function, that will lead to better treatments of neurological and psychiatric disorders. Thank you very much.

TB: Thank you very much for sharing this information with us, and for contributing to the training of many of the participants of this meeting.

IK: Well, it was just being there at the right time, and it was, as I said, a privilege and a pleasure.

TB: You were the right man at the right place at the right time.

IK: Thank you.

41. CONAN KORNETSKY

TB: We are in San Juan, Puerto Rico. It is December 10, 2003. I will be interviewing Dr. Conan Kornetsky⁴³ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let's just start from the very beginning. Where are you from?

CK: I was born in Portland, Maine, on February 9, 1926, the third child of Alex and Ida Kornetsky. My siblings were a sister, 12 years older and a brother 14 years older. Due to an error by the obstetrician, my mother died a week after my birth. During the first year of my life, we lived in a large three family house with the families of my mother's two sisters. After a year, my father gathered up our family and moved to Chelsea, a suburb of Boston. Because he could not take care of me and work, I was boarded out to another family. After two years, my father remarried and we were all together once more. This lasted for a couple of years before my stepmother died of cancer, when I was in kindergarten. From that time until I finished third grade I was a "latch key child." During those years, during the depression, we moved every year around Boston because landlords would give you 12 months to live in an apartment for 11 month's rent; moving was a great savings. I did kindergarten through third grade in the Boston area; my sister graduated from high school and my brother from the Massachusetts school of optometry. But, my father could not find work in the Boston area. My sister went to live with one aunt in Portland, I with an aunt and uncle who had no children. My brother took a job in northern Maine with an optometrist and my father found a job in a shoe factory in Auburn, Maine. I stayed with my aunt and uncle through high school. Although they tried their best, I was not a happy child. They correctly saw me as difficult. I loved to read but was not a good student. I was fairly independent. I loved history, mathematics, and science but I didn't do well in those subjects. I used to argue with the teachers and if you disagreed with the teachers, you were thrown out of the classroom and had to spend time in the principal's or Sub-Master's office. The Sub-Master and I became very friendly; he used to get me back in the classroom and worked out some apology with the teacher.

⁴³ Conan Kornetsky was born in Portland, Maine in 1926. He received his Ph.D. from the University of Kentucky while working at the Clinical Psychology Department at the US Public Health Hospital, in Lexington, Kentucky. After post-doctoral work at NYU and Mt. Sinai Hospital, he moved to the Intramural Research Program of the National Institute of Mental Health. Subsequently, he joined the faculty of the Departments of Psychiatry and Pharmacology at Boston University School of Medicine. He was interviewed in San Juan, Puerto Rico on December 10, 2003.

TB: When did you graduate?

CK: I graduated high school, in 1943, and entered the University of Maine in engineering, in June. World War II was on, so I tried to get time in college before I went into the service.

TB: How old were you when you graduated?

CK: I was seventeen years old and did one year of college by January 1944. Then, I was inducted into the US Army, Air Force, in March. I was supposed to train as a navigator but due to cutbacks they gave me temporary training as an engineer on B24 bombers, while I was waiting to be trained as a pilot or a navigator. When the war ended, they gave me a choice of early discharge or pilot training with three additional years in the service. I decided that was not a good choice, so I was discharged.

TB: When were you discharged?

CK: In December 1945 and I went back to the University of Maine, in January 1946. I decided I didn't want to be an engineer, so I went into a liberal arts program and decided to look into various fields. I took a lot of philosophy, history, and psychology, found psychology and philosophy the most interesting and received my degree in psychology, in 1948. I had a number of interviews but couldn't find any job that was satisfactory. At that time, the GI Bill would pay for further education; first I thought I would go to graduate school in philosophy. Then, I decided I would not be able to earn a living if I did that, so as a second choice I thought clinical psychology would be interesting. I had taken an intensive course in testing that certified me as a mental tester. I had also taken a course in abnormal psychology, in which we visited a local state hospital a number of times, where patients with different diagnoses were presented. So, I looked into the American Psychological Association's listing of approved schools for clinical psychology.

TB: What did you find?

CK: The only school approved in New England was Yale. Approved schools elsewhere were all first rate but I was not that good a student; I had a mixed academic record in college. I did very well in courses I liked, but in courses I didn't like I didn't care what grade I got. Also, I was very active politically after the war. I was a member of the American Veterans Committee, which was a radical leftist group. I was more interested in politics than grades. I had a professor of philosophy and religion and we used to go to a local pub and argue. His aim was to prove that God existed and my aim was to prove God did not exist. Every paper I wrote for him was to prove that. We

had a great relationship and he said, "See if the University of Kentucky is an approved school." He used to teach there and wrote me a good recommendation. So, I applied and with his recommendation I was admitted into the clinical psychology program.

TB: When was that?

CK: I arrived in September 1948. I had the GI Bill but after a few weeks I wanted to find an additional source of funding. The GI Bill paid for books and tuition, plus a stipend. I got a job in a sorority house as a house-boy, a glorified janitor. But then, the Chairman of the Department told me there was an opening for one student in the Clinical Psychology Department at the US Public Health Hospital, in Lexington, Kentucky. This was a hospital for the treatment of drug addicts. At that time, I did not know what a drug addict was and the only drug I knew about was alcohol. I didn't know anyone who used marijuana. However, I had to make a choice, sorority house or a mental tester; so I took the job as tester. The stipend was board, room, and laundry; so, I would live at the hospital. The Lexington USPHS Hospital was also a prison for the incarceration of addicts. It was a great experience living there. My room was a cell similar to the cells of the prisoner-patients. The only difference was that I had a key to my cell. I didn't have a car, but transportation was fine. It was five miles from the University. There was no trouble getting back and forth during the day, but in the evening I was stuck there, so I used to study and hang around and chat with the prisoners, who would tell me all about drug use.

TB: That had to be interesting.

CK: I found the most interesting place to hang out was the research ward. I spent time talking to the patients and learned what experiments they were on. I was learning a lot; I don't know if I believed all the stories, but they were interesting. The director of research was Harris Isbell. He would make rounds every evening and he kept seeing me there. After he learned who I was, he would tell me about the experiments, including a new clinical experiment that he was planning on chronic barbiturate intoxication.

TB: This was what year?

CK: The fall of 1948. At that time, it was not known there was physical dependence to barbiturates. They knew there were sometimes convulsions and seizures, but no one had ever demonstrated if that was withdrawal or intoxication. So, he was planning to do a study. Because he had no psychologist, he asked me if I would be willing to participate. My main job was that

every afternoon, I would do three Wechsler IQ tests on patients and write them up. I still had to do that, but I started to participate in the study. This was pretty heavy stuff for a first year graduate student. I knew IQ testing and a few new tests that I was picking up in graduate school. As a first year student, I was pretty skilled in IQ testing. I developed further one of the sub-tests on the Wechsler, so we could use it repeatedly. It was the Digit Symbol Substitution Test. What I did was to change the code every time they took the test. Although there would be a practice effect, there was no learning of the number-symbol code. I probably broke all sorts of copyright laws. I also used projective tests that I was learning to use that were popular. There was a resident in psychiatry participating and Dr. Isbell, a technician, and myself. I was basically the third professional, the psychologist on the project, which was great.

TB: It was your first professional experience in research?

CK: That was my first professional experience as a researcher. I spent most of that year participating in the experiment and writing my results. During that year, I learned a great deal about the behavioral and pharmacological effects of addicting drugs. One of the missions of the Research Department was to test new drugs for addiction liability and physical dependence, as well as analgesic potency. They never found one, but that was the mission. Nathan Eddy from the National Research Council would come periodically with a bag full of new drugs to try on patients. These were prisoner patients who would volunteer. They would be given drugs under controlled conditions and were followed very closely to determine if physical dependence developed.

TB: How many subjects were included in a typical experiment?

CK: There were a few subjects in each experiment. There were six in the barbiturate experiment. One of them quit. What we found was that besides continuous intoxication, during abrupt withdrawal from daily administration, all the subjects had convulsions or a psychosis. That was the first demonstration there was physical dependence to barbiturates, and it was the first publication with my name on it: Isbell, Altschul, Kornetsky, Eisenman, Flanary, and Fraser in the *Archives of Neurology and Psychiatry*, 1950. Isbell urged me to write a separate paper giving more details of my results. I did, turning in a hand-written manuscript of about a hundred pages. Well, my section covers two published pages in the original paper. Isbell was very kind; he taught me how to whittle it down and it was published as a separate paper. He insisted that for my career it was better if I will be the only author. The title of the paper was, "Psychological Effects of Chronic

Barbiturate Intoxication.” It was published also in the *Archives of Neurology and Psychiatry*, in 1951. It was all heady stuff for me.

In June of 1949, I was married to Marcia Smargon, in Boston. Marcia and I were classmates at the University of Maine. During the academic year 1948-1949, she was a graduate student in social work at Boston University. By the time I returned to Lexington with my bride, Abe Wikler had returned from his yearlong sabbatical. Because the stipend of board, room, and laundry was no longer applicable, now that I was married, Harris Isbell hired me as a technician, from money he didn't need for an animal caretaker. So, I would be paid from now on as a technician and was hoping that I wouldn't have to do anymore IQ testing.

TB: So you had enough from IQ testing?

CK: I was getting disenchanted. One of the things I was trying to do was psychotherapy but I found I didn't like it. I found it interesting at first, but by the third time I saw a patient, I was bored. My wife still didn't have her degree, but she got a job in the child guidance clinic as a social worker with the professor of clinical psychology. This was probably good for me. My first contact with Wikler did not create the impression I would have liked. Although Dr. Wikler had been back from sabbatical for only a couple of weeks, he had already started experiments in which he measured autonomic responses and reflexes in dogs after drug administration. These were recorded on smoked kymograph paper stretched between two “drums.” A stylus operated through changes in air pressure that would move the stylus back and forth on the smoked paper. He would later shellac the paper to make a permanent record. In the course of this process, these paper loops were hung on pegs outside his office and until they were shellacked they were vulnerable. I came bouncing into his laboratory to meet the famous Abe and when I inadvertently brushed against some of the smoked paper loops, I heard a scream from Abe, “who the hell is this stupid ass?” That was my first contact with Abe, who later became my close friend, mentor, and colleague. After he realized who I was and that I wasn't stupid, we became very close friends. Another person came on the research staff in the summer of 1949, a psychologist named Harris Hill. Isbell assigned me to work with Harris Hill and we did some early studies on anxiety, analgesia, and morphine. Abe would run an informal morning seminar. So, every morning, we would meet over coffee and he would give the seminar. We would have discussion groups deciding on experiments; that is where I proposed what I thought was the greatest experiment in the world. It was probably the

proposal I'm most proud of because it was a very early demonstration that environmental factors could affect the way a drug acted. What I proposed was a simple reaction time study in which we would change the motivation of the subject during the reaction time. The hypothesis was that changing the motivation of the subject would alter the way morphine would act on reaction time. I proposed this and Abe had a way of quizzically looking at you and the more he looked the more stupid you felt. Finally, Abe was very direct and said it was a stupid idea. The master had spoken, but a week later he bumped into me in the corridor and said it was a great idea; but we had to change it a bit. We did the experiment and it turned out as I predicted. In the presence of anxiety precipitated by a situation in which the subject did not know whether he would receive the punishing electric shock until the "go" light appeared, behavior became disorganized and reaction time was slowed. That led to a series of experiments in which we measured pain threshold under different environmental conditions, with and without morphine. I spent three years doing those experiments with Abe and Harris Hill. My dissertation was on the effect of morphine and the role of environmental factors on the perception of pain.

TB: What did you use for producing pain?

CK: Radiant heat on the forehead and I measured pain threshold using classical psychophysical means, which hadn't been done before.

TB: So you studied the interaction of environmental factors and morphine on the perception of pain?

CK: By manipulating the environment, just prior to the experiment. Basically, it consisted of establishing rapport with the subject by spending about fifteen minutes prior to the experiment in friendly conversation. We did a whole series of experiments, but mine were unique because I measured autonomic responses, verbal reports, and used classic psychophysical means. That was my Ph.D. dissertation. Abe was the director of that dissertation, but because he did not have a faculty appointment at the time, he was not the one who signed off on the thesis.

TB: When did you get your degree?

CK: In 1952, and then I moved on. At the time I was doing my dissertation, I was involved in other experiments. There was a big increase in juvenile drug addiction and a young psychiatrist, Donald Gerard, came to Lexington. He and I were assigned to study juvenile drug addicts. We did this for about a year and a half. Then, it was decided we had to do a follow-up study in a large

urban area and we picked New York. So, in the fall, we moved to New York and we studied juvenile addicts, in 1952 and 1953. We probably did the first controlled study of juvenile addicts; it was interesting because our control group consisted of friends of addicts. The big problem we had was finding friends who were not addicts themselves. It took us a year to get 22 “friends.”

As Dr. Gerard and I were the so-called experts on drug addiction, having been at Lexington, we were asked to help Dr. Isidore Chein, in the Department of Social Relations, at NYU, to get started on a big NIMH sponsored study of juvenile addiction that led to the book, *The Road to H*. Don Gerard, after our year of study of the friends of juvenile drug addicts, took a position with Chein and was one of the co-authors of the book. That is probably the best social psychological study of juvenile addiction in a large urban area. The book starts out with the sentence; “H is for Heaven, H is for Hell, H is for Heroin.” During my last year at the Lexington Hospital, my status changed. At that time, I was an officer in the U.S. Army reserves, and when the Korean War started, I was called to active duty, in 1944 -1945. Because I was not eager to go into the Army again, Harris Isbell had me transferred from the Army to the USPHS commissioned corps, which was still part of the armed forces, a holdover from WWII.

TB: What did you do after the completion of the juvenile addiction study in New York?

CK: At the completion of the juvenile addiction study, I was asked to spend another year in New York to study LSD with Murray Jarvik at Mt. Sinai Hospital and with Harold Abramson at Long Island Biologic Laboratory. Then, in 1954, I moved to NIMH in the intramural program at Bethesda. I was there from 1954 to 1959, in Seymour Kety’s Laboratory of Clinical Science. In the laboratory next to mine was Julius Axelrod. In fact, I needed some temporary lab space at one time, and Julie had a little space he allowed me to use. Anyway, I did a series of studies on the effects of psychoactive drugs on performance. First, I studied the effects of chlorpromazine, analgesics, barbiturates, and opiates in humans. I also did sleep deprivation studies. Some of those I did with Alan Mirsky. He and I developed a hyper-arousal theory of schizophrenia, namely that the schizophrenic was in a state of hyper-arousal, and not hypo-arousal, due to a filtering problem. The idea came from studies performed in the mid 1950s to the 1970s, working with the Continuous Performance Test (CPT), in which I found that amphetamine did not improve performance of subjects who were functioning at full capacity. Their performance was actually impaired by amphetamine.

TB: Could you tell us something about the CPT?

CK: The CPT was a straight vigilance task. Random series of letters were presented on a screen at a constant rate and the subject was required to press a simple lever, whenever an X appeared. You could make it more difficult, by requiring pressing the lever for the X, only if it follows an A. During the 1950's, the only effective drug for the treatment of schizophrenia was chlorpromazine. We found that chlorpromazine would impair performance on the CPT, but not on the Digit Symbol Substitution Test (DSST). We would then compare the findings with chlorpromazine with the effects of a barbiturate. Barbiturate produced no impairment on the CPT, but a clear impairment on the DSST. It was a clear dissociation between these two tests in normal subjects. We then went on to study schizophrenic subjects. We found that schizophrenic subjects performed as well as normal subjects on the DSST but were markedly impaired on the test of attention, the CPT. Mirsky and I were lucky at that time because the schizophrenics we studied had not been chronically receiving neuroleptics.

TB: Didn't you do some studies with amphetamine in schizophrenics?

CK: Much of the work I did with amphetamines in schizophrenics was after I came to Boston University, in 1959. During this period, I administered single doses of d-amphetamine to chronic schizophrenics and I did not see any exacerbation of symptoms. I started measuring blood pressure effects and I kept pushing the dose up and finally at 40 mg of amphetamine, I had to stop because of increased blood pressure. There were no other effects. Our CPT studies with Alan Mirsky had already demonstrated that a major deficit seen in schizophrenics was the trouble of focusing and filtering stimuli. Since in normal subjects, amphetamine allows you to filter and focus, I thought it might improve behavior in schizophrenics. So, I proposed, at Medfield State Hospital, an experiment in which I would chronically administer amphetamine. Harry Freeman, Director of Research, was all for that study. However, the committee that was equivalent to present IRBs was not enthusiastic. They said I would have to do a pilot study before they would give permission for a more elaborate study. They allowed the administration of 20 milligram of oral d-amphetamines to the subjects in the evening. Although they predicted that the patients would be climbing the walls, they gave permission for one week with a crossover to placebo for the second week. Half the subjects received the amphetamine the first week and a placebo the second week. It was reversed for the other half of the subjects. Although we were interested in sleep behavior, we did

not have the facilities to monitor sleep. We had the nurses, on the hour observe each subject and score them with a plus (+) if they appeared to be sleeping and with a minus (-) if they appeared not to be sleeping. I did not want the nurses to ask if they were sleeping. One of the subjects quit, so I was left with 9 subjects. Compared to placebo, there was no difference between the treatments. With amphetamine, 3 subjects looked like they were sleeping more, 3 looked like they were sleeping less, and 3 showed no change. They certainly did not exhibit a potentiation of their schizophrenic symptoms or exhibit excitation from the amphetamine. The nurses reported no difference in behavior when the subjects were administered amphetamine. Whether they had shown any cognitive or other improvement I don't know.

TB: You said this study was done after you returned to Boston.

CK: This was the late 1960's. In 1970, when I presented these data, nobody paid attention to it. I asked Danny Freedman, who was the editor of the *Archives of General Psychiatry*, if he was interested in publishing this paper; so, in 1978, the paper was published with the title "Hyporesponsivity of Chronic Schizophrenic Patients to Dextroamphetamine." As before, nobody paid attention to it. Getting back to chlorpromazine, my question was how could schizophrenics get better if the drug decreased arousal that would impair normal people. Allan Mirsky and I postulated an inverted U hypothesis of arousal, so that where you are on that curve determines your response to amphetamine. We plot along the abscissa the arousal level, and if the normal person is on the ascending side of the inverted U and you administer amphetamine it results in an increase in arousal. If the person is on the descending side of the U, over-arousal, then amphetamine would move him further on the descending side and cause a decrease in arousal. Thus amphetamine has the same basic pharmacological effect in normal subjects and schizophrenics, moving both to the right, increased arousal; however, the actual response depends whether you are on the ascending or descending leg of the inverted U. If you are on the left side of the peak, and you are given a drug, you become impaired. Since schizophrenics are over the hump, if you give them a drug they do better. Now that is an over simplification. But our belief was that there are some schizophrenics who are like that; and that there is a filtering problem. I did a number of studies with Marissa Orzack in the 1960s and showed that some first-degree relatives of schizophrenics responded in the same way as some schizophrenic patients. The nicest study was that of Gerry Wholberg. He was a psychiatrist and a research fellow at Boston

University. The question he asked was whether our findings are dependent on a state or a trait. So, he took patients on medication and in good remission, and gave them the CPT test. First, he did not find any impairment on the CPT. Then he decided to do the test in a situation in which the patients were distracted by a noise. He did this in schizophrenics in good remission and with normal subjects after he did a recorded interview. He found that schizophrenic patients, exposed to an interfering noise, did not do well on the test. They were holding jobs, functioning people out in the world in good remission, yet they showed impairment when he added the noise because they couldn't filter well. I thought that was a fantastic study. Yet for some reason, nobody paid much attention to the findings. I believe because it did not fit with the main stream of thinking at the time.

TB: Did Gerry Wholberg follow up his findings?

CK: Gerry left and took a job as Director of Clinical Training at Boston State Hospital, when one of his residents saw a paranoid patient who left against medical advice. The patient returned and wanted to see the resident. When the patient was alone with the resident, he pulled a gun out of his pocket and pointed at him. They were in a room with a small window in the door. When a nurse saw the gun she called Gerry. Gerry felt responsible because it was his resident and went in the room. He talked for three hours with the patient. Finally, when he thought the patient was about to give up the gun, the patient pulled the trigger. The bullet hit him in the head. He lingered for a month before he died.

TB: Why didn't you follow it up?

CK: I was having trouble getting funded for my schizophrenia research. They just weren't funding it, so I focused on the drug abuse. I was mainly interested in tolerance and did a lot of work with Joe Cochin, on single dose tolerance. Our argument was, once you experience a drug, there is going to be some residual tolerance. There was a study done, when I was in Lexington by Frank Frazier, in which he found that drug addicts, six months after their last dose, show tolerance to a single dose of morphine. He needed normal volunteers for his study, so I volunteered, and as a subject received a single dose of 20 mg of morphine intramuscularly. I must admit that I got a high on it. I really liked it. However, I didn't want to try it again because I didn't like the loss of control.

TB: Would you like to say something about your recent research?

CK: I'm interested in two things, aging and opiates and have been working in these two areas for two years now. I'm working on the effects of analgesics on the reward system in aging. The general belief is that older people need less morphine to produce the same analgesic effect. I don't believe that, and my findings are in the opposite direction. I have a small grant to do preliminary work; that is coming to an end and I am writing grants to do more in this area. I am very interested in this research. I think research with analgesics is very important and I also think older people are under-medicated. I'm also working with alcohol. I am still active.

TB: What would you like to see happen in your area of research in the future?

CK: As I grow older, I am bothered by some of the things I hear. I would like to see more attention paid to science and less to money. What is driving science now is not the excitement, but something else, and that is bothersome. I get excited when I see something new. I love it when the students get excited looking at data.

TB: On this note we should conclude this interview with Dr. Conan Kornetsky. Thank you, Conan, for sharing this information with us.

CK: I enjoyed it. Thank you, Tom.

42. STEPHEN H. KOSLOW

TB: We are at the 38th Annual Meeting of the American College of Neuropsychopharmacology in Acapulco, Mexico. It is December 15, 1999. I will be interviewing Dr. Stephen H. Koslow⁴⁴ for the American College of Neuropsychopharmacology. I am Thomas Ban. Could you tell us where you were born, brought up, and something about your early interests and education?

SK: I was born in New York City, spending all of my childhood years there going to school. I went to college at Columbia University. After I graduated, I left New York for the first time and went to Chicago. What brought me to Chicago was the University of Chicago. I was enrolled in the Department of Pharmacology to study psychopharmacology, get a Ph.D. degree, and pursue the area of brain research. This is an area that has always interested me and I thought it was the most challenging in terms of all scientific areas.

TB: Who was the Chairman of Pharmacology at the time?

SK: The Chair was Lloyd Roth and he was also my Ph.D. mentor. He was interested in using radioactive tracers to look at distributions of drugs in the brain and he developed some very sophisticated audio/radiographic methods. He had done whole body radiography, and then, he developed a cellular method for autoradiography, so he could look at where the drugs localized at the cellular sites. He was a great mentor; and the department focused on the central nervous system and neuropharmacology. To my knowledge, in those days, there was not much around in terms of neuropharmacology. There were few texts to speak of. It was really the beginning of the modern era of brain research and the University of Chicago had some great scientists who showed us and taught us how to think about how the brain might operate and gave us a good chance to get into the field of brain research.

TB: Could you tell us about brain research in those days? Am I correct that we are in the early 1960s?

⁴⁴ Stephen H. Koslow was born in New York City, New York in 1940. He received his Ph.D. from the University of Chicago in Pharmacology. After postdoctoral training at the Karolinska Institute, in Stockholm, Sweden, he joined the Intramural Research Program of National Institute of Mental Health at Saint Elizabeth's Hospital. He, subsequently, became involved in administration of the Extramural Research Program of NIMH. He was interviewed in Acapulco, Mexico on December 15, 1999.

SK: I was at the University of Chicago from 1962 through 1967. In those days, brain research was really a black box, no matter where you studied; even if you were in laboratories looking at how drugs worked. At that time, we had, what probably looks now to be a trivial argument, whether serotonin, norepinephrine, and dopamine were neurotransmitters and whether they really existed in the nerves and functioned as neurotransmitters. These are the things I grew up on; learning about how the brain worked. We thought at that time that we had a great deal of knowledge and understanding in terms of brain mechanisms and how drugs worked in the brain.

TB: What was your dissertation on?

SK: My dissertation dealt with anticonvulsant drugs and their site of action in the brain. This was my real first research experience. This research led me to believe that it was important to study drug mechanism of action at the cellular level. After I finished my degree at the University in 1967, I had a post-doctoral fellowship in Sweden. What I wanted to do was to look at how drugs worked at the cellular level. There was a researcher at the Karolinska Institute, Dr. Enzo Giacobini, who was studying single cells from the nervous system. He was isolating them and studying how they functioned biochemically. He agreed that I could come and study how anticonvulsant drugs acted at the cellular level. Well, no surprise it was not really possible to do the specific study that I wanted to do but going to the Karolinska Institute for a couple of years was a very rich experience. It was really great to have the exposure to the Swedish community and in particular the Karolinska scientific community and to the variety of brain research that was being done there.

TB: Could you tell us about what you learned?

SK: I learned how to isolate single cells and look at microchemistry of cells. And I also became interested in neuronal regeneration. We did some interesting regeneration experiments in the peripheral nervous system, reconnecting different nerves to each other, and looking at their function and chemistry. Many of the people that I worked with there made it a very rewarding, rich experience.

TB: With whom did you work?

SK: My post-doctoral sponsor was Dr. Enzo Giacobini. Among those I interacted with at the Karolinska Institute were Thomas Hoekfelt, Lars Olsen, and Urban Ungerstadt. It was an outstanding opportunity to interact with people making important contributions to the

understanding of brain function, to understanding the morphology, cellular connections, and chemistry of the brain. The big question was what to do when I returned to the US. I was interviewed by Mimo Costa, who headed a key research group in the Intramural Research Program of NIMH at Saint Elizabeth's Hospital. He was just developing a big research program there and he offered me the possibility to come back as a Fellow and work with him. He liked some of the things we were doing in regeneration. He also believed that it was important to do studies at the cellular level. On returning to the U.S., I came back to Dr. Costa's group at Saint Elizabeth's Hospital in Washington, D.C. On the personal side, while in Sweden, we had our first child, a daughter. We came back to the United States with a Swedish baby, so to speak, and settled in Maryland to allow me to work at Saint Elizabeth's for a number of years.

TB: Could you tell us about the research you did at Saint Elizabeth's?

SK: I continued to do research on regeneration. Dr. Costa asked me to develop chemical methods for looking at small quantities of messenger RNA. He asked me to do this because he felt it was very important to have this capability to extend his research, which at the time was focused on neuronal neurotransmitter turnover rate. At that time, there were no methods to look at small quantities of mRNA. The research went exceedingly slowly. There was also a chemist in the laboratory, looking at gas chromatographic mass spectrometric methods to do the same thing. Dr. Costa suggested that we work together and try to develop quantitative methods for measuring extremely small quantities/concentrations of neurotransmitters. Within a short period of time, Flaminio Cattabeni and I managed to develop a very sensitive quantitative method to look at the major neurotransmitters, which, at the time, were serotonin, norepinephrine, and dopamine and their metabolites. We proceeded to develop this method and did some interesting studies to demonstrate where neurotransmitters were in the brain, even if not quite at a cellular level, but close to cellular level. We used a new term to define our quantitative sensitivity. This was femtomole, reflecting the low concentrations we were able to measure. That was a busy period in my life. My wife was going back to school to get a degree in psychology; we had our second child, and, as you know, when you work in a lab you spend many hours there. It was an extremely productive period developing new methods and approaches to study the brain. But, I felt at that time, that I was getting narrow in my pursuit, and needed to stand back to be able to look at theoretical issues. To overcome this deficiency, I accepted a position in the extramural research

program at NIMH. The position was in the clinical research branch. The Head of the branch was Dr. Martin Katz, who is also a member of the ACNP.

TB: What was your assignment in the clinical research branch?

SK: I was responsible for making decisions about funding and stimulating the development of research in the field of biological psychiatry. The branch in which I worked funded biological approaches to clinical problems, and I had responsibility for the basic research focus in the branch. This was fascinating because it gave me an opportunity to learn about the clinical side of mental illnesses and meet with some of the outstanding research leaders of that day and get some insight into what their research and problems were about. This was a real growth period in terms of expanding my horizons about how the brain worked, and also how clinicians looked at the brain and thought about understanding mental disorders. During that period, Dr. Martin Katz was working with Drs. James Maas and John Davis and others to develop a multicenter study to look at experimental approaches to study the biology of depression. At that time, all of the theories of depression were derived from small studies in which biogenic amines were a central theme. In those studies, the biogenic amines may not have been measured with the greatest accuracy and the diagnostic procedures were different from one study to another. There were many neurochemical theories of depression. Marty, Jim, and John designed a study that would test these hypotheses in a large population of individuals using a new standardized diagnostic system across all of the research sites. They brought together scientists who had expertise in endocrinology, biochemistry, and clinical diagnosis and designed an in hospital study with depressed patients along with a normal control group. The study started with a washout period for both patients and controls. Patients and controls were evaluated using the same protocol and the patients were re-evaluated after pharmacotherapy by measuring biochemical and behavioral changes. It wasn't an experimental study to develop new drugs, but rather it was testing the effects of existing effective drugs. We used tricyclic antidepressants and studied behavior, and biochemical measures in cerebrospinal fluid and urine, as well as endocrine changes. It was a fantastic experience to be responsible for coordinating this study. We did the study over a five year period. We had 150 depressed subjects, who were treated and about 80 normal healthy controls. Both groups went through the same baseline procedures. The findings were interesting, but I guess, disappointing.

TB: Why were the findings disappointing?

SK: Because, they didn't support the major existing hypotheses, but rather added to the controversy. While it was clear there were disturbances, based on the measures taken, they were not as major as people thought they would be, and it remained unclear what the exact alterations are in the disease. We really couldn't support any of the biochemical hypotheses, creating chaos in our thinking and in the thinking of others. Another major controversy arising from this study was whether it takes two to three weeks for the drug to start to work, as suggested on the basis of other clinical and basic neuropharmacological research. The behavioral findings are based, for example, on Hamilton Depression Rating Scale scores, a very global measure of symptoms in depression and not on fine measures of behavior. In our study, we looked the Hamilton scores, as well as more refined measures of behavior, and we saw that early on, soon after treatment began, patients started to change in terms of their anxiety ratings and other symptoms, all decreasing in intensity, before changes were noted in the more global Hamilton scores. I think this is a major issue that needs to be researched more carefully. There is a need to include more refined behavioral measures in clinical studies to be able to look at the behavioral components of the disorders, not just the global clinical measures of depression. Unfortunately, when we designed the study, we used the published literature as our guide and looked for changes that could take place after two weeks of drug therapy. All the biochemical measures were taken at baseline and then two weeks after drug therapy. Luckily, we had behavioral measures on a daily basis. So, we could see from the behavioral measures that the changes started pretty much soon after drug treatment initiation. Marty is following up this issue, to answer the question whether the drugs start the recovery process early on, as we believe the data demonstrated in our in study.

TB: Would it then be correct to say that your data did not support biochemical theories of depression and about the mode of action of antidepressants? Would it be correct to say that your data showed detectable treatment effects without a two to three weeks delay, shortly after commencement of treatment?

SK: That is true. The study was very rewarding in terms what we learned from it. We published our findings and the ACNP provided an excellent forum for discussing with other scientists about what our findings meant. At the time that study was conducted, I still had other responsibilities of stimulating and funding grants in biological psychiatry at the Institute. But while coordinating the study, I was also able to return to my major interest: how basic brain functions operate.

TB: Are we in the late 1970s?

SK: This is now around the early 1980s, and by that time, it was clear to me, a basic neuroscientist, that the NIMH should invest more money in basic neuroscience. I convinced the institute leadership to think about creating an extramural program for funding neuroscience and a Neuroscience Research Branch. They did create it in 1983, and I became the first branch chief. I proceeded to develop a program in Neuroscience to look at basic brain mechanisms in order to better understand the functional pathology of mental disorders. This program developed quite nicely over the next seven years. Each year there were more neuroscientists and more questions to be answered. It was a great experience and opportunity to develop this program. In the 1980s, the molecular biology revolution was beginning. We tried to introduce people into this area of research. It was very stimulating and rewarding to see people start to move in the new directions using molecular approaches. I think the program did extremely well; one could see the field changing. It was also reflected in the ACNP, which became much neuroscience oriented, and less clinical, to the unhappiness of some members and the happiness of some others.

TB: So, you think that the implementation of your program played a role in the move from clinical research to neuroscience in ACNP meetings.

SK: I think there was a group of us that wanted to see psychiatry based on biology. Initially, I thought it was a good meeting because I could learn about the clinical aspects of brain research and disorders, but I wanted to see more information on how the brain actually works transmitted to clinicians. During this period, I also promoted efforts at the NIMH to support research on imaging. Imaging offers a unique window on the brain; that could allow us to do innovative studies. I think by now, everyone understands that imaging is a powerful tool for understanding the brain in health and disease. We are still struggling with the methodology of imaging because however powerful, it still has limitations. Now, there are multiple ways to image the brain that are more powerful than what we had in the '80s, which was limited at that time to positron emission tomography. When Lew Judd became Director of the Institute, he was interested in seeing neuroscience applications in psychiatry grow even more rapidly. He created a Division of Neuroscience and I was appointed as the Director of this new division. Given this opportunity, we developed many more research programs. There was greater investment in supporting research on understanding the brain from the point of view of molecular mechanisms. This was exciting. It

was also the beginning of the Decade of the Brain; a marvelous period of pursuing knowledge about how the brain works. There were an increasing number of people interested in pursuing brain research. There are currently about 30,000 people, who attend neuroscience meetings annually in the United States. If you think about the type and amount of data that is generated by all these people, it is enormously rich. I'm saying this because this is really where my focus is now at the Institute; trying to stimulate the field to do research in specific new areas. The issue basically is that, at this point in time, with all of the advances in technology and approaches to study brain function, we have a richness of data that isn't totally utilized by everyone, even by the researchers who have created the data. Most people will do experiments to answer a specific question and once they answer that question and publish the paper, the data is usually put on a shelf someplace and never looked at again. But, if one wanted to reanalyze the data or ask slightly different questions, you could do that if the data were available. The way we do research today, they are not available. I believe that we are in the middle of a very exciting new revolution.

TB: What revolution are you referring to?

SK: The information technology revolution. We are all impacted by it in every way and state of our lives. We need to take advantage of the new technology and do something different in the way we do science. We need to have a paradigm shift in how science is carried out and allow our data to be shared more universally and allow our data to be mined by other scientists. It is not only the amount of data that creates this need, but also the way neuroscience and brain research is done today. Because of the complexity of the brain and the highly specialized technology used, it is very difficult to study the brain as an intact organ. This doesn't allow you to look across levels of function, across levels of analysis. Look at the journals that are published in neuroscience research today. There are some very broad journals like *Brain Research* and *Journal of Neuroscience*, and then there are journals restricted to the synapse, hippocampus, etc. This specialization has led to fractionation of the data. As a field, we need to try to rebuild the brain from all of the fractionated data that we have in order to understand how the brain works because this fractionated approach is not going to have as quick of a payoff as if we were able to put all of the data back together again and look at it in term of systems and whole brain function. We are collecting data at an extremely rapid rate; there are 200 brain research journals published each month. Anyone who writes a grant application or a paper needs to spend days, if not weeks, in the

library trying to recover data from the literature. If we were using modern IT we could hit a button to have all of that data come to your PC, and that would be fantastic and liberating. To be able to manipulate and re-analyze original raw data would be even better. To accomplish this, the NIMH started a program, in 1993, called “The Human Brain” project; we now also call it Neuroinformatics.

TB: What is the objective of the new program?

SK: The goal of this program is to set up databases that would be on a distributed system and be accessible via the Web, using search browsers that can pull data into your computer and, then, you can create your own unique database to query specific questions of the data. This would be similar to what has occurred in genomics, where bioinformatics has led to the creation of national databases of the human genome and other genomes from different species. But, for all the data that exists in neuroscience, it would be too large of a database to try and centralize it. We currently believe that the best approach is to set up a system of distributed databases, where each investigator or group of investigators can get together and create a database for each data type they are working on in their own data model. Since everyone likely has their individual model, in across data models, there would be overlapping areas that could be used to fuse data across levels of analysis and to combine data to look at how brain function might be integrated. Another important aspect is the understanding of the complexity of the brain. We have to be able to construct theoretical mathematical models. We have seen models developed for ion channels of individual neurons. There are now unique mathematical model platforms, which allow one to plug in different experimental values to explore nerve cell function under different conditions. By using theoretical mathematical models, we can go back and forth between experiments and theory and push experiments further through queries of the model. From what you learn in this approach, you go back and change the model. It is an iterative process of building a greater understanding of how systems work. We need to have models from single neuron levels, from the gene level up through the systems level, and ultimately the whole brain in order to truly understand the brain. This approach should help put the different pieces back together again. At this point, I find this one of the most exciting challenges and opportunities for the field of science. I think people are slowly starting to agree that this is important to do, but many people are resistant because they worry about sharing data.

TB: Sharing data is a sensitive issue?

SK: A frequent question I get when I talk about this program is: you mean you want someone else to look at my data? And, I say, yes, that is true. Scientists are concerned that others will find out a different answer by looking at the same data that may be true. The reality is, if someone can reanalyze someone else's data and come up with a different possible answer that may move us forward. For this to happen would require a paradigm shift in both the way individuals think about someone else looking at their data and also about the way we reward the scientific endeavor. Currently, scientists are evaluated and rewarded for journal publications. I don't believe this should change. When we think about sharing data, we agree that individuals should publish their data first and then share their data, and not share it before they publish it. The scientific vetting through peer review is critical prior to data sharing. If this sharing of data works, then, we also have to give rewards for people who create databases and contribute to databases, to people who create some of the algorithms for models and not just for publishing scientific results. This can be a stumbling block because it has to be built into the system, both at the university level, in terms of promotion, and also in the grant review mechanism, when evaluating a person's career. I find this a most exciting and challenging opportunity.

TB: Did you ever return to laboratory research?

SK: I never went back to lab research, but instead, stayed with the NIMH extramural programs. I made this decision because it is a unique opportunity to contribute to science in a way that you could not do in the lab. It is very stimulating to try and see what new opportunities are there and how the field can best use them to move forward in brain exploration. It has been rewarding to see that what you think is right and suggest to the field, that they embrace it. It doesn't always happen, but most of the time it does, and it's great to see the field move forward.

I didn't have the need to go back and work at a bench to feel that I was scientifically involved, invested, and making a significant contribution in advancing the field of brain research. I felt it was very important for our field to have a representative voice within the NIMH. It was a rich experience to be able to do this. It has been great fun, extremely rewarding to see the field moving; the frustration is the slowness with which it moves. If I look back at my career at the Institute, I was trying to push imaging, in the early 1980s, and remember a lot of starts and false

starts, and now it is a major research focus and everyone wants to do it. It has produced great new insights into brain function and mental illnesses.

TB: During the past 30 years or so, you collaborated with many people. Would you like to mention by name a few?

SK: I have been fortunate and honored to have the opportunity to work and interact with many great scientists and leading researchers. I already mentioned my mentor at the University of Chicago and Marty Katz, at NIMH, who taught me a lot. But, also working with Mimo Costa was a marvelous experience. He is a great scientist and intellectually engaging. He is a very warm person, who taught me a lot about how to think about how the brain works and how to design critical experiments to answer questions. It was a great shaping effect about the way I think about the brain. So, he was terrific. In the collaborative program, I established great working relationships and friendships with some of the outstanding scientists in psychiatric research, like Jim Maas, Peter Stokes, John Davis, and a whole bunch of people who are now mainstream researchers, like Charlie Bowden, Regina Casper, Alan Frazer, and Jim Kocsis. The ACNP has given me the opportunity to meet a lot of top researchers in the field and to learn from them and to take what I've learned from them and apply it to my job to try and help move the field forward. It has been a great opportunity to work at the Institute and to have the opportunity to impact on the field in a unique way. From my perspective, it's been just as enriching as working in a laboratory and pursuing your own interests and understanding how the brain works.

TB: Are you pleased with the progress you are making in your program?

SK: It is progressing at a reasonable rate. In the United States, we have about 20 grants that are funded to create databases and the needed electronic tools for data sharing. These activities are forming the nexus for neuroinformatics. To make this work, it has to occur globally, because research is done around the world. We have established a working group with the European Commission of the European Union. They are now funding, in Europe, similar types of neuroinformatics research and we coordinate their research with the research done in this country. They now have funded, for example, one consortium of workers who are creating a database on the cerebral cortex. This will be a fascinating database that will integrate the data from the different areas of research related to the cerebral cortex, including connectivity, electrophysiology, pathology, etc. I have also been working with a working group at the OECD. As you probably

know, the OECD was established in Paris after World War II to help Europe recover economically from the war. In the 1990s, they started the Mega Science Forum that organized meetings around common scientific problems and provided recommendations on their resolution. Most of the discussions dealt at the beginning with the field of physics, but in '95, they expanded to include other fields. At that time, the U.S. proposed a working group in neuroinformatics. It was accepted and we have worked with other countries around the globe to start programs in Neuroinformatics. This program is taking on its own life and it is exciting to see that it is happening globally.

TB: So, by now I assume there are databases being created in many areas?

SK: Yes, we have a number of grants now that are funded to create databases for imaging, electrophysiological data, neurotransmitters, and receptor systems, and so on. In the next month, I have an organizational meeting with about 50 scientists to discuss central organizational issues in neuroinformatics and how to organize a grant submission to establish an International database on cognitive function. At this meeting, we will also be discussing how to organize similar efforts along all the clinical science and research areas.

TB: How long have you been in your current position?

SK: I now have a new position at the Institute, which is Associate Director and Head of the Office of Neuroinformatics, because this is the area where I want to focus and concentrate on.

TB: Could we switch to your involvement with ACNP? When did you become a member? SK: I have been a member of the ACNP since 1976 or 1977. This has been one of my favorite organizations. I have served on many ACNP committees.

TB: On which committees did you serve?

SK: I chaired for one year the program committee and I served also on the credentials committee. And Marty and I, in the late 1970s and '80s, convinced the ACNP to start its own journal. It is rewarding to see that the Journal now has its own life and is doing well.

TB: So, it was you and Marty who suggested that ACNP should have a journal?

SK: Yes, we suggested and talked to a lot of people to help make it happen.

TB: Would you like to mention some other organizations you have been involved with?

SK: I participate in Neuroscience, but not to the same degree.

TB: Are you involved with any of the neuroscience journals?

SK: I sit on a number of editorial boards. I was on the editorial board of the ACNP journal at

the beginning and now serve on the board of an imaging and a pharmacology journal. There are a couple of computer journal editorial boards I also serve on. It is always fun. But, it is hard to see what kind of impact you have on those journals.

TB: What would you consider as your most important responsibility in your job?

SK: My philosophy in working in the federal government is that it's our job to look to the future and ensure that the resources are there for scientists to do their work. It is my responsibility to make things happen to generate new interests and exposures.

TB: What would you like to see happen in the future?

SK: There are a couple of things that I would like to see happen. I would like to see more groups get together to create databases focused on specific areas. We could take any of the sessions here, and in each, there is a group of investigators who could work together to create a database. One of the problems in doing this is that we have the scientific expertise, but we don't have the expertise on informatics. This will require scientists to establish relationships with informatics scientists to make it work, to build the right types of databases. Most of the databases that we have today are built for financial and business communities, and our data doesn't easily fit into those types of databases. It is going to take extra work to find a computer scientist to work with to create the database. I believe that it is extremely important to have a database for every class of drugs. Would we have that we would have all of the basic data used in publication in one place and you could retrieve it, re-analyze it from your own perspective. When you start to think of the elements of such a database, it gets huge. I think you have to start with many small unique databases that you can draw from. There was a session yesterday at this meeting, for example, that dealt with the anatomy, connectivity, and the function of different circuitries in normal brains and in disease states. It would be a wonderful database to have all of that information available in a searchable database. There is not one and we have to create it. To do that, we have developed a unique mechanism to support database creation. We also are offering grant support for people to create courses in Neuroinformatics and to provide training in Neuroinformatics as well as career awards in Neuroinformatics to support scientists in their postdoctoral years to get training in Neuroinformatics. We should also help to develop scientists who are not neuroscientists or information scientists but Neuroinformatics researchers. They would have cross training in computer and neuroscience. What I see as the ultimate goal is that you turn on your PC at home

or in the office and by pointing and clicking on brain areas you can get whatever type of information you want ranging from genes to behavior and then you can zoom in on that information and can fit your own data to it. You could examine the data in any way you would like, but, that is down the road, we are not there yet. We need everyone contributing the data and building this informatics resource.

TB: Everyone contributing from around the world?

SK: Yes, definitely so. It has to be worldwide, if it is going to work. It won't work if just from people in the United States join this effort. I don't know what the numbers are for psychology, but for neuroscience in this country we have approximately 25,00 to 30,000 people and worldwide there are 50,000 to 55,000 neuroscientists. Some of them are psychiatrists and neurologists. If we could bring all of the information, all the data, from all these brain scientists together, we would have extremely valuable data.

TB: Is there anything else you would like to add?

SK: Not at this time. I appreciate this opportunity to review my scientific activities with the ACNP.

TB: Then we should conclude this interview with Dr. Stephen Koslow. Thank you for sharing all this information with us.

SK: Thank you.

43. PAUL LEBER

TB: This will be an interview with Dr. Paul Leber⁴⁵ for the Archives of the American College of Neuropsychopharmacology. It is December 1999; we are at the annual meeting of the College in Acapulco, Mexico. I am Thomas Ban. Could you start with by telling us about your background and education?

PL: I'm the son of a physician, and I think it was understood from the time I was very young that the only sensible career was probably one in medicine. I toyed with other ideas, but basically, I think the long-standing parental model held, and before I knew it, I was a physician.

TB: That was when?

PL: I graduated, in 1963, from NYU School of Medicine, but I was ambivalent even then about what I wanted to do. I thought about it because I had taken what was the forerunner of M.D., Ph.D. programs. I had a medical sciences degree and during that period, approximately two and a half years, I spent in the lab basically looking at the biochemistry of myosin ATPase. And that, I say, represents my ambivalence. I already had been on the wards at Bellevue and found the clinical care of patients in a charity hospital not at all that I had thought it would be. Having seen medicine through the eyes of my father, who was a practicing physician -- if you'll recall the book, *The Last Angry Man* by Green, describing the life of a practitioner -- it was not what I saw in the wards of a big city hospital and I decided that there might be other ways to make use of my background.

At that time, Lew Thomas, who was the Chair of Medicine at NYU, had started something called the Honors Program that was an attempt to get young medical students who might otherwise have gone directly into clinical practice, into the medical sciences. This was in the post-Sputnik era, where there was great interest in developing research capability in all areas and it was fairly easy to get grant money from the Federal government. I think that stimulated the general belief that anyone going into practice was probably foolish, that the real career in medicine wasn't to become

⁴⁵ Paul Leber was born in Brooklyn, New York in 1937. He received his M.D. from New York University School of Medicine. After an internship at Johns Hopkins School of Medicine, he returned to New York University and transitioned to a residency in pathology. He first became a member of the faculty of the Department of Pathology at the State University of New York at Buffalo, New York, and then, the Department of Pathology at Harvard Medical School in Boston, Massachusetts. He completed a psychiatry residency in Cornell University at New York Hospital, Westchester Division, White Plains, New York. After a short time on the faculty of Bellevue Psychiatric Hospital in New York City, he joined the Food and Drug Administration in Washington, District of Columbia. He was interviewed in Acapulco, Mexico on December 15, 1999.

a clinician but become an investigator. I think that to some extent, I got caught up in that role model and that's how I shifted away from the idea of being a physician. It was the first time I'd probably thought about what the distinction meant between the role of a physician and an investigator. I think there was still a bit of a sense in me that physicians were different and special, as they were at least in my father's eyes. He probably struggled a lot harder than I did to get things in his life. But some of the bloom was off the rose by the late 1950s or early '60s, and I think the feeling was that just being a clinician wasn't all that unique or different. The feeling was that we were science and medicine and solving mankind's ills through chemistry was somewhat appealing to me. So I ended up, finding myself half a biochemist and half of a fledgling physician. I was advised by most of the people, who knew me at the time, to get a very strong clinical background.

TB: Where did you do your internship?

PL: I interned at Johns Hopkins in Baltimore. I spent a year there, and I usually say that I still owe them for that year, during which we arduously took calls on rotation, when we were on the ward. I came back for a year of residency in medicine at Bellevue and by then, I was pretty much sure that the actual delivery of healthcare at that level wasn't what I wanted, and I went into pathology. Pathology at that time was the kind of place where people who couldn't actually relate to patients went. It was a way to do the basic science of medicine without having the demands of patient care. And patient care in the charity hospital system, if you really want to do it well, was a full-time activity. It was the actual care of patients plus roundsmanship that meant you devoted your life to doing it, unless you became an academician and did research. And to many of my friends, it seemed more reasonable to do it in an area where you could regulate your university academic responsibilities, as you could in pathology. The basic science you ended up doing was the same, basically, at least so I thought, early in my career. It turned out later that I recognized the control was very much in the hands of the clinicians and not pathologists. And one of the reasons I eventually, I think, switched fields is that I really didn't want to work for other physicians, a strange comment. But at the time, pathology offered a lot of advantages. I didn't want to quite give up medicine, but I wanted to take advantage of what I had learned before, and pathology seemed a reasonable compromise. It's true, pathologists are somewhat isolated, but in the American set-up, being a clinical pathologist afforded you some contact with other physicians that at one time was seen by me as a great advantage.

Subsequently, having worked for surgeons and others, I adopted a view that pathologists were the physicians' physicians. Unfortunately, they are in the sense that a valet is a gentleman's gentleman. So there was a fair amount of service to other people and not so much control. And I started to drift towards psychiatry.

In about 1969, I went to State University of New York at Buffalo following actually Bob McCluskey, the guy that I had worked under as Chief Resident of Pathology, who moved to Buffalo and became Chairman of the Department of Pathology of the University Hospital. I went to Buffalo as the person who was going to coordinate the courses for the second year students in both medicine and dental school, while doing also some work in the laboratory. While my major academic responsibilities were not in the clinic or even in the path lab but running the courses, I found that we were having a lot of difficulty with students. This was the time when they were trying to increase the number of students being graduated from medical schools. There were many programs to bring disadvantaged students into the University, and the school was not doing all that well. And one of the missions, obviously, of the pathology department, which was sort of the introduction to medicine, was to improve the school's Board scores. I got involved in this, and we managed to improve the scores, but we still had a block of students that were doing very badly. And I have to say, in dealing with them while on the faculty at Buffalo and discussing problem students that we were ordered to pass to the next year, I became impressed that I could handle them as well as anybody else. This was one of the factors that contributed to my drifting from pathology to psychiatry. Added to that was the fact that I'm married to a clinical psychologist.

TB: So, you are married to a psychologist?

PL: She was trained in sort of an analytically style, and I always had what I thought was common sense about things in psychiatry. But in any case, it was probably a lingering idea to become a psychiatrist. Anyway, McCluskey left Buffalo in 1971. He went to Harvard and assumed the Chair of the Department of Pathology of Children's Hospital there. Although I had no interest in pediatrics per se, it seemed appropriate, when offered a job, to accept at 'America's best medical school.' My life was pretty pleasant in Buffalo. I had a lab. I had my teaching that I liked. I was doing renal pathology in those days, which was the area I had moved into. But there were also some hindrances, as for example, the horrible winters. Anyway, for whatever reason, I ended up on the faculty at Harvard Medical School in the Department of Pathology. But after three years of

working for surgeons and working in basically a position where I didn't quite fit in the system, I had become fairly disillusioned with what was going on in pathology and discovered that I really didn't like it at all and began to think what else I might do. We always joke about people having midlife crises. I guess I changed careers, and I think my experience in Buffalo plus exposure to my wife, got me interested in what was going on in psychiatry.

TB: So, you decided to do a residency in psychiatry.

PL: By that time, my experience in pathology and my understanding of some reductionistic explanations in medicine made me increasingly cynical about what objective medicine could offer. I think by then, I was convinced that much of medicine was practiced on the basis of old wives tales, told from one clinician to the next. A lot of what we did was what we did because our professors did it. Pathology, like psychiatry, shares a diagnostic system that is taxonomic, authoritarian, and passed down on the basis of convention rather than real understanding. And even though I didn't realize all of that, I saw pathology as a discipline that had reached its peak in the 19th century, in histological pathology, and I wasn't really that satisfied with that. Anyway, whatever the real reasons are, I decided, with my wife's acceptance of this, perhaps she could have saved me and I would have never been a psychiatrist, to retrain. And that was in about 1974.

TB: Where did you do your residency?

PL: Where I landed up doing my training was probably just chance. I began to look at opportunities but I had been through enough residencies in internal medicine and pathology, to be a connoisseur of what one really needs. I recognized that simply being on call all-night and having a very tight schedule, just make you very tired and doesn't teach you much. So, I ended up at the New York Hospital, Cornell, in the Westchester Division, which is one of those hospitals, all very much alike, built at a certain period of time in the United States. They have large, pleasant campuses that remind you of something between a country club and a private school. They really were built at a time when psychiatry was seen as an asylum for those who could afford it, to remove themselves from the Sturm and Drang of everyday life into a commune with squirrels and nature, to take a rest cure modified by changes in fashion, offering water or hydrotherapy, or whatever the fashion was of the time. But basically, they were asylums in the sense of gloom and doom. And this particular hospital in Westchester had, at that time, perhaps 240 acres. It was very attractive and had the added advantage, since I came with children and a wife, that it would give me a house

on the grounds. I didn't get much salary, but basically I could afford to retrain from what I got, and that probably determined where I went, as much as anything else. I didn't necessarily want to go to a place that was a big city hospital again. So I ended up in Westchester at the time when it was undergoing a transition. It was an eclectic background that I got at Cornell. In fact, it surprisingly had gone through a period where it had supported almost anything but analytical views. One of the people who was at Westchester before I came but had already left by the time I got there, was Paul McHugh, who was an advocate of the phenomenological school that was competing with the analytical. These were the dying days of psychoanalysis, although it would have been hard to say at that time that psychoanalysis was dying. But eventually, it happened at Cornell. In any case, I was hired by a group of eclecticists who were still there after McHugh had left. But then, at about the very same time, Bob Michels brought the remnants of the Columbia Psychoanalytic School faculty to Cornell. So, it was a very strange time. We had on the faculty people who basically ascribed to Jaspersian phenomenology, mixed in with people who were card-carrying doctrinaire analysts. It was, so, a fascinating time. We had the psychoanalytic faculty coming in, who wanted people who got directly into psychiatric internships without probably ever taking care of a patient. So, we had people coming in without any background in medicine, mixed with a lot of older people among the residents, who like myself, had come from other fields and decided that a more holistic view of mankind was worthwhile, and were re-training. Then Otto Kernberg came.

TB: When did he come?

PL: He came towards the end of my last year. I did my whole psychiatric training there, three years. But by the time I completed my training, I was totally disillusioned with psychiatry. I had dealt with a number of the prominent people in analytical psychiatry. Their methodology always left me somewhat aghast. They would say, let me have two TATs and a Rorschach, and I'll tell you whether a patient is schizophrenic. Now, when everybody knows that a patient is schizophrenic on the basis of some common conventional code, it's fine; but when you have somebody who is a little peculiar and they decide on the basis of some response to a questionable test, I was somewhat offended by it. And by then, I was finished with the whole concept of the psychoanalytical model and was much more interested in biological psychiatry. It had nothing to do with the place. The place wasn't biologically oriented at all. The one unique thing that the

training program had offered was the remnant of McHugh's influence. They spent an awful lot of time talking about the phenomenology. For me, the most useful part of the training was sitting around in a room with my colleagues, looking and talking to patients, watching their behavior, and then afterwards, discussing what we saw. If there was any group that was against explaining what they saw, it was the group of phenomenologists. They simply wanted to describe what they saw. So that was very useful. But all what the analysts were interested in was to get us into analysis.

TB: Did they get you into analysis?

PL: I spent some time doing analytical training, and if anything, it embittered me. Well, the first thing they said to you, when you didn't do something they liked was that you have countertransference. I once pointed out to one of the professors that he had, himself, a countertransference reaction directed at me. Now, of course, psychoanalysis wasn't so dominant in the program that they could order you to go into analysis but if you disagreed with them, they tried to make you feel that something was obviously wrong with you. It was a kind of catch 22. And it was difficult to deal with them because they still had some power. They did convince me that I needed to get back to a real hospital.

TB: So, you wanted to get back to work in a real hospital.

PL: I was interested in liaison psychiatry because it, again, was a way to make use of my background. I still liked many aspects of medicine. So I ended up trying to get a job in liaison psychiatry. There were some openings available, but not in locations I wanted to move. So, I went to Bellevue. It was the one place where I still had many people that I knew quite well in the departments of medicine, physiology, and pathology because I had been there for some 13 years on and off. It was like going home.

TB: Could you tell us something about Bellevue Hospital at that time?

PL: All right. I can elaborate a little bit about Bellevue Hospital Psychiatric Service, at the time. I actually had been there twice. In 1965, when I was a resident in medicine, I spent some time in psychiatry there on a rotation. This was before the Health and Hospital Corporation took over the city hospital system. At that time, the Bellevue Psychiatric Hospital, which had a physical bed census of 430, used to run in-house, at any given time, perhaps 600 to 650 patients. If you walked through the wards at night, on the upper floors, where the acutely psychotic and seriously ill patients were housed, you saw mattresses spread along the floor because the hospital just did not

have enough beds. The psychiatrists could not serve the large mass of patients who flowed through Bellevue because the hospital was the last resort for almost everybody from everywhere. When a major New York hospital, like Columbia or Cornell, refused to admit someone, the patient was brought to Bellevue. If there was any hint that the patient might not be a medical patient, and patients often were not, they were sent up to the psychiatric hospital, where they had sort of a prima facie evaluation but little else. A lot of people were misdiagnosed for psychiatric patients who weren't, and you actually did some good by correcting the diagnosis. Well there are many interesting internal old Bellevue stories, some of them probably apocryphal, more than real, but basically there was always a struggle because of the enormous load, beyond everyone's capacity to cope with. Things were somewhat improved when I came back, in 1977. After the Health and Hospital Corporation took the hospital over, they were trying to put caps on the size of the wards, but clearly, they would still have overflow. And there was just not sufficient support. We didn't have a psychiatric nurse on our ward. The ward originally had a U shape, and we were supposed to have two nursing stations, one facing down each arm. Because we didn't have staff, we could not have aides, so they closed one of the nursing stations. That meant that one arm of the U was basically unsupervised bedlam, where assaults and various other things took place. I once went to the Medical Director of the hospital to complain, after a particularly difficult morning, where there had been a fight in the dining room and some of the inmates had broken off bits of the edges of the tables and carving on the tables knife-like devices. The Medical Director said, well, Paul, you really should be concerned because you are responsible.

TB: What kind of patients did you see at Bellevue?

PL: Well, when I was there in '65, as a medical resident, I would say that the vast majority of patients admitted to the hospital were classified as schizophrenic. But, at that time, American psychiatry was in the bloom of its analytical mode. Diagnosis was unidimensional and based more on somebody's feelings of what a patient had. So all chronic patients were just immediately called schizophrenic. We didn't have time to do a mental status exam. We were just overwhelmed by very bizarre presentations, some of which were medical, and some of which weren't. Things had changed a bit by '77 because the analytical movement was losing grounds.

TB: Were you aware that DSM-III was just around the corner at that time?

PL: Oh sure. We knew that DSM-III was coming already when I was in Westchester.

TB: You started to tell us that most patients at Bellevue were diagnosed as schizophrenics. What about affective disorder?

PL: We had no patients diagnosed with affective disorder. We got the patient from the New York bus terminal, the ones who were found wandering, who were bizarre. We got the homeless, those with chronic brain disease, people who were disadvantaged. We didn't get a representation of the psychiatric population. If you got to Bellevue, the only one drug you could get there was Thorazine (chlorpromazine). It was usually delivered IM in large doses so that people would be knocked out. I didn't have, myself, a great knowledge or experience with drugs. I had been brought up on homeopathic doses of haloperidol in the Westchester division, where the last thing they wanted you to do was medicate someone. As a matter of fact, the phenomenologists were treating their patients with barbiturates for a few days to see whether or not the psychotic process would disappear, so that we might see the underlying personality.

TB: So the situation at Bellevue in those years was pretty bad.

PB: Yes, and after spending almost a year at Bellevue, I decided that I'd had it. Dealing with the frustrations of a city hospital system, living in Westchester, and having a small part-time practice in midtown, was really just not what I had retrained to do. Liaison was an area in which most of the people wanted to get Fellows to do the work, but it wasn't an easy and sure way to establish yourself. In fact, you often ended up in a consultative, rather than a truly liaison system. And just at the time I was wondering about what I should do, I learned about a possible job with the FDA. The FDA was, at the time, a place that people, with the exception of those who worked there, knew little about. It's an organization, that at least until the time of David Kessler, operated more behind the scenes than in front. And I came down to Washington, in 1977, to look at the job.

TB: What made you decide to take the job with FDA?

PL: As I had said earlier, the FDA was as much an unknown agency to me, as to anyone else. I came to the FDA not because I had a cause, but because it seemed to be a good place to make use of my background. It was a place for someone who knew something about medicine, pathology, and psychiatry. I felt, in a way that it would allow me, in mid-life, to do something that was constructive and useful. And I have to say the FDA has been a career for me. I've been there 16 years. It is probably the place where I've learned most and felt I was doing the most. I know now very clearly, how little one really can do within a relatively weak mandate that it has.

TB: So, your motivation was to do something constructive and useful.

PL: I think motivation is complex and it isn't what caused me to go to the FDA; but, what I did once I got there, I think, was important. I went into a job that I suppose some could have treated as a 9 to 5 job, doing the reviews and leaving. I work 60 to 70 hours a week. I like what I do. I find the area I'm working in fascinating. I'm involved in it because I see it as a microcosm of our society, where I can make something happen that's good, do the right thing. I'm imperiled to do the right thing. And what I can add is that in doing the right thing, one has to be as an umpire, who is never that popular because when he makes his calls, he is always offending someone. I must have been the subject of several editorials in the Wall Street Journal, stating either that I was not caring about patients or that I was industry's boy. But I know that I care about the patients by carrying out my job under our law; that even if I do this in a somewhat paternalistic way, I want to make certain that the drugs are reasonably safe when used under the conditions they are recommended. But what I like about the agency is that it's a place that tries to do the right thing, with a fairly clear set of directions. My response to the libertarian argument to let the marketplace find out whether a drug is safe, and to use tort liability to handle unsafe drugs, is that our society hasn't agreed on that compromise and Congress is free to change our laws anytime it wants to do so. Personally, I think it would be a mistake. I actually think it's a very good idea to have rules of pre-market clearance that establishes that a drug is not excessively dangerous, that it probably has a reasonable risk benefit ratio, and so on. It is intervention by government, but that's the nature of our existing laws. It's easier for me to enforce it because I believe in it. It doesn't mean that I don't have moments of tension, where I see where the law doesn't exactly fit.

TB: Can you give an example when the law doesn't exactly fit?

PL: If we have to tell some patient with advanced ALS, look, we're concerned about allowing you to have access to this experimental drug, for which we have no evidence of effectiveness.

TB: I suppose the same applies to AIDS?

PL: When I came to the agency, AIDS was just about beginning to be identified as a distinct syndrome.

TB: Before moving any further, could you tell us what the mandate of the FDA is?

PL: If you look back over the last 100 years, you see a pathway to produce a government that is protective against the forces that may take advantage of the consumer and gets the government to

step in and do something about that. It's related to the philosophy that government has to protect the citizen from situations that are beyond the citizen's control. It's a kind of delegated narcissism, that the government can do more than actually it can. Congress is always passing a new law that adds greater protection. To a certain extent, protection, because of the way it's sold, looms larger and seems to have more power than it actually does. The task is to make sure that all drugs are safe and effective for use. But what does that really mean? No drug is safe and no drug is fully effective. People want things that they haven't thought through carefully. So we talk about offering protections, without knowing all that is involved. But there certainly has been a trend in this country to produce a society where individuals are protected from the unlimited power of certain groups or institutions. And no doubt, it's the role of the government to do that. So, more and more powers were given, but also, more and more demands were placed upon the agency to help ensure the safety of the consumer, at least in terms of the products that society allows to be marked as food, drugs, and cosmetics. Now, whether or not the agency can cope with the task given, considering the number of products out there and given the number of opportunities for things to go wrong, even if one is careful, is another matter. You see many things can go wrong with a drug, even if you do a wonderful job. And we have a public that is inflamed if anything goes wrong. They are good news stories, regardless whether they have any basis. And we have a public that is inflamed by these stories.

TB: Could you say something about what you have been doing since you joined the Agency?

PB: I came, in 1978, and I was assigned to be just a medical officer. Within a year, I became a group leader. Actually, I became a group leader because I was thinking about leaving. It was kind of boring what I was doing and the then head of the department said look, you're bored by the job, tell you what, why don't you become a group leader and try to do something to make it better. And I was involved with antipsychotics and anxiolytics, and somebody else had antidepressants. I wasn't even involved with hypnotics. We also had Tom Hayes, who wasn't a psychiatrist; he was in neuropathology. We may have had one other psychiatrist in the unit. And I began looking at trial designs, and it became fairly obvious to me that one can't conclude anything from trials that fail to show a difference. Bob Temple was making a similar point, and we thought that if we were going to make a judgment whether a drug worked, we ought to make it on the basis of the difference from something because finding similarities prove little. This didn't come from me. It

came from Modell, who had taught it in pharmacology, in the 1940s and 50's, before we had efficacy requirements. They said, look, you shouldn't conclude anything about a clinical trial unless you have the ability to discriminate the active substance from the inert one. That's absolutely the basis of the argument. So I found myself in the position where I could start imposing that the law says that one has to be able to conclude that the drug is effective, and that one is not supposed to conclude that on the basis of evidence that is ambiguous. It was the need to provide evidence that lead to the use of the placebo in clinical trials. Then, by 1985, we developed a new trial design that lead to greater flexibility. That document pretty much summarizes what I think were my contribution in the area of designing clinical trials.

TB: So, by 1985, a new trial design was developed that lead to greater flexibility.

PL: At that point, we got caught up in AIDS, and the desire to have early access to treatment became dominant, and that undermined our ability of find critical evidence of a difference for a new treatment. We ran into this issue a couple of years ago with a football player for the Jets, Dennis Byrd, who was injured in a Sunday game at Giants Stadium. He was quadriplegic after the accident and ended up getting a drug product made by FIDIA, one of the gangliosides. He could get it because, at that time, it happened that we had something equivalent to a compassion protocol that allowed the use of a drug before its effectiveness is conclusively proven. And while the Dennis Byrd case was going on, we had a randomized controlled trial that involved randomization of people with spinal cord trauma. Now Dennis Byrd happened to do fairly well, whether because of the steroids he got, the ganglioside, or simply by chance, I'll never know. But the mere knowledge that this guy had access directly to that drug without running the gauntlet of randomization, created a humane cry that threatened the investigators doing the trial. I got some of the most compelling letters I've ever seen, saying, how could my child be forced to go through randomization, when this guy with connections didn't have to. Well, a lot of the diseases that we are dealing with, not so much in psychiatry but in neurology, have no effective treatments, and as a result, people with those diseases say well, what have I got to lose given the active substance; I have the right to ask for whatever it is; it's my life. They say I want the new drug now; how dare you stand in my way. And with this kind of arguments, the issue of autonomy that dominates thinking about ethics in medicine today becomes a central issue. Now all this sounds very grandiose because if it's your child in pain, you want to get access to the medication without randomization.

TB: How does the agency handles the requests?

PL: What people really want is access to a drug; and what the Agency decided that everyone should at least have equal access by randomization, 50% probability of being exposed is better than none.

TB: Are you in a decision making position?

PL: I'm only a small cog in a very, very large institution that is making decisions with several tiers of supervision and safety nets, and the like. I may offer an opinion, but my opinion isn't necessarily taken. Actually, most of these drugs that I'm accused of approving against the interest of the public, I don't even approve. All I do is forward a set of recommendations, offering my view about whether or not the evidence presented was gained from sources that nominally look OK and whether or not our review supports it. I usually try to defend what we do, not because I believe that I need to defend it, but because I think the institution has to be able to explain why it took a particular position.

TB: What is the most common accusation?

PL: The most common thing that is said about the people in the FDA, is that they're in a poorly paying job and after they work there a few years, they get bought by the industry and move over to well paid jobs. But whom are they talking about? Well. Name one? Supposedly, there is a string of people from the FDA, who supposedly moved over to industry, and then, spend their time helping the industry prepare their drug applications. I'm sure that every institution has its ogres and has its angels. I'm sure that there are a great variety of individuals. The vast majority of people who work in my unit haven't gone anywhere. They are still there. I'm there 16 years. The head of the neurology group is there 11 years. The head of the psychotropic group is there 11 years. They are the people who're making the major policy decisions. The only ones I know about, by the way, who went to industry to high paying jobs recently, in our area, were lawyers. They go to industry. They go and work for other corporations, but they were never involved in deciding whether drugs worked or not.

TB: Let me ask you what do you think of the common complaints that complying with all regulations interferes with work?

PL: It comes down to people on the clinical side saying, well we've got to go through all these good clinical practice procedures now and spend so much time filling out papers that we don't

have the time to look and listen to our patient, to make those key discoveries that were made through close observation of patients. And people within the industry are saying that I used to work on the bench, but now with these good laboratory practice procedures, I've become a manager who's trying to ensure that every piece of paper gets saved, so that we can pile up all these papers onto huge trucks which go off to the FDA, and all of this is getting in the way of being able to create and design. I don't believe in any of this. The idea that the physician looks at the patient and says, aha, this is a new syndrome, I don't believe. I think a lot of this is political polemics. There's no doubt there is plenty wrong with the regulations. It's like Churchill's line about democracy: It's a lousy form of government, but there's no better.

TB: One of the drugs in psychiatry that was affected by regulations was clozapine. I know that you had been involved in the clozapine story. Could you comment on that?

PL: Clozapine is a good example of a drug that astute clinicians recognized might be different than other drugs. The problem was that until there was evidence provided that it was different, there was little one could do about it. And had it been a drug that hadn't been associated with agranulocytosis, probably it would have been approved, and no one would have had any knowledge about whether it really was better than any of the other drugs, except by word of mouth. Because of the high risk of giving clozapine, it was necessary to show that the drug might have some advantages over other neuroleptics. This led to the demonstration that it was an effective treatment in patients non-responsive to high doses of haloperidol, and that was actually to the advantage of the company that was manufacturing the drug. I don't know how good really clozapine is because all I know now is the testimony of people, who apparently were unable to function in the community before, and now are able to do so. But at least, we have some basis now to believe those stories are true on the basis of the evidence that came from a controlled trial. I wish there were ways to get long-term outcomes and to know if the findings of that study are really true. At the time when the clozapine patient management system was put in place, I don't think it was our intent, in any way, to restrain trade. It was simply a way to ensure that there would be no patient treated without monitoring leukocyte counts. We were very concerned that we might have one of those public health disasters. It ended up that several people interpreted it as an attempt to restrain trade, and we had other parts of our own government examining it. Eventually the Federal Trade Commission, I believe, impelled Sandoz to adopt a more open system of distribution. The

more I think on the clozapine issue, the more it seems that it had created a new treatment resistant inpatient category.

TB: Are you saying that clozapine created a new diagnostic subcategory used as an indication by the industry?

PL: Absolutely. No doubt we may have created an indication that doesn't exist. I don't feel all that badly, however, because a good part of psychiatric diagnosis, we all know, is nothing more than people agreeing that they will call the dough of nature what they want to call it. I'm still trying to find out who said that a good part of psychiatric diagnosis is taking a cookie cutter to the dough of nature.

TB: I don't know. I haven't heard that one. Some believe that the aim of diagnosis is to carve nature at its joints.

PL: I think that we may have created a subgroup that is nothing more than the tail of distribution. It may not be constant. I have no idea whether it breeds true, but it was created by our attempt to balance benefit and risk. It may turn out that what we did was not a wise thing to do, but I think given the information we had at the time, it was a responsible thing to do. That doesn't mean that other people could not have done it differently. There is always more than one way of doing things. We try to find the right way, and anyone who disagrees, has a variety of ways to disagree with our way. We're obviously working in a world where there's absolutely no certainty. You're always making some kind of judgment, you're always trying to find a way to accommodate a variety of forces, a variety of beliefs, and you are always trying to do the right thing to work within the restraints of the law, in the time you live in. And I'm sure that you cannot possibly satisfy everybody. Clearly, the aims of every industrial developer of a drug are not the same as of the patients, who would like to have a perfect medicine, at a low price, and available instantaneously. They are incompatible goals. It is probably not possible to have drugs that are reasonably safe, adequately labeled, and unlikely to cause harm, at least in excess, without having regulatory controls.

TB: What do you think about current attempts of having quality of life as an acceptable measure of outcome?

PL: Well, quality of life, I've always thought, is a grandiose, sweeping statement. We're all interested in things like beauty and truth. We all demand it. The problem is we don't all know it

when we see it. I think quality of life is a very valuable goal. The problem is that I'm not sure you can measure it when you're talking about a particular disease entity. You certainly would like to have measures of global outcomes and general benefits, or something of that sort. The problem is when you call it quality of life. A lot of the quality of life rating assessments, as I understand it, were developed first by social health planners, who were working across a spectrum of illnesses and disabilities with the objective to decide where to put societal funds and energies. I guess if you want to compare the disability of prostatism with that of breast cancer, with that of chronic schizophrenia, having some measure that is not disease specific, it makes some sense. From the standpoint of regulators who are interested in whether or not the drug is effective for a particular disease, quality of life measures are more questionable. It would be more relevant to get something in terms of the impairments and disabilities associated with that particular disease entity. I wouldn't call it quality of life. I would go out and find what it is in that entity. I guess I'm a little bit concerned about anything that's too global, sweeping, and grandiose a statement that is on everyone's lips. It's a good way for third party payers to be snookered into paying for more expensive drugs. But it's very hard to know how one weighs the various elements that go into quality of life; they may include rating assessment on anything from how much one enjoys leisure time activities, to whether or not one has adequate housing. I think we are better off using measures of the pathologies, disabilities, and impairments that we are dealing with than quality of life measures.

TB: Regardless of the end-points used, if I understood you correctly, you are for randomized clinical trials.

PL: I often wonder how anyone can adjust without a randomized controlled trial for the fundamental differences that could arise in outcome research between the reason people are treated with the drug and the disease they have and the nature of the drug treatment they receive. I guess I'm an old stick in the mud, I like randomization and randomized control trials, not because I believe that randomization solves all evils, it just minimizes the biases we don't know about. Short of randomization, I don't know how anyone guarantees the differences seen are due to the nominal application of this one thing you're interested in.

TB: What are your thoughts about the need for comparative studies?

PL: I'm always afraid of comparison. I mean how to compare new drug products, I think, is one of the biggest problems we face today in the wars that are going on between cost benefit and cost effectiveness. In some ways, a new drug starts with a handicap and not only because the developing of a new drug is more expensive in 1990 than it was in 1980. How do you get on the market and recover your costs in a contracted world? You have to say you're better than somebody else. What makes you better? Well, are you better than every product in the armamentarium or better only than some? What are you better for? What are the dimensions on which you make comparisons? There are literally an infinite number of ways you can compare drug products. You might compare the quality of effects, their intensity, their times of onset, or their duration. How do you pick which of those dimensions you're going to look at? Well the clever marketer of a drug identifies an area where the market would stand improvement and shows that his drug is better than drug X. So, in case of an antipsychotic, he might compare the effect of the new drug in producing EPS with that of haloperidol, which has a probably well-deserved reputation for causing a lot of EPS. Is it fair, therefore, to conclude that the new drug is better than antipsychotics, in general, because it beat haloperidol in producing EPS? How do you know what an equally effective dose of two neuroleptics is? Somebody says 10 mg of haloperidol is worth of 6 mg of risperidone, whereas someone else would say 20 mg haloperidol is worth 6 mg of risperidone. And probably, the biggest problem is that very often people will pick the conditions of comparisons to suit their goals, and we, as regulators, are going to get involved in this kind of problem. One just has to be very careful that the comparisons are fair.

TB: What are your thoughts about the use of fixed or flexible doses in clinical drug trials?

PL: You'd probably want a fixed dose but these days, fixed dose is coming into a lot of criticism, and with good reasons.

TB: What are your thoughts about sample sizes, the need for large sample sizes?

PL: They are certainly going to be necessary, but the methodology for doing them fairly in a way that gives you information that doesn't mislead you is going to be tough, and I don't think we've worked it out yet. Well, the basic problem is that we don't know the etiology and pathogenesis of most of the phenomenon that are subsumed under the diagnostic group of recommended conditions. Not only that, it's not clear whether a medical model is really the best. I'd be the first to acknowledge that one of the difficulties with taking the medical model very seriously in

psychiatry is that the medical model grew out of a belief that the cause of disease was univariant, that you had a pathogen that interacted with a host and generated perhaps some psychopathological features. The concept of multifactorial, polygenic model doesn't suit too well the medical model, which says that these are like medical diseases that have their etiology and their causes. Now for purposes of making progress, I always thought DSM-III was a great idea because it allowed people to use a common set of definitions. It allowed people, at least, to agree on what they were describing. It has created the possibility of doing experiments. You can, at least, recapture or resample and you can find out whether the populations are biologically homogenous, in terms of their response, or not. I'm not sure whether DSM-III, DSM-III-R or DSM-IV are real advantages to anybody being labeled or just another taxonomic system. But again, I'm talking about this from the point of view of someone who wants to develop a treatment. I want to be able to communicate what that treatment is for in a way that other people will understand.

TB: So, you are in favor of the DSMs?

PL: For communication purposes, and I think to that extent, you're stuck if you want to decide whether the labeling is accurate and not false or misleading. How would you communicate without it? It would be idiosyncratic and impossible to communicate if we would not use it. Clearly, these drugs aren't used by psychiatrists alone, but are used by GP's for a variety of things. We felt it would be very useful if we could give them a fairly standard description and that's all it's intended to be. And of course, in this society, technically, a physician is free to use any approved drug for any reason they want, provided it's allowable under the jurisdiction of safe practice. That's an issue people are increasingly confused about, it seems. People feel that if a drug had been licensed for a certain use, then one is on tricky grounds of using it for other indications.

TB: Yes.

PL: We have frequently been chided for failing to approve drugs for uses everyone uses them for. Xanax was widely used for a long time in panic disorder without any labeling. We were concerned about higher doses and the difficulty withdrawing from the product, and we decided that it would be useful to examine these issues, first, before handling the claim for that indication. The argument was that panic was always subsumed within anxiety or generalized anxiety and people could treat it any way they wanted. In fact, there are some investigators who believe that panic disorder doesn't exist, and if it does exist, it is just as treatable with other benzodiazepines as it is with

alprazolam. But all of that being said, there is certainly an advantage to us to be able to make clear cut distinctions between what we have evidence for and what is common usage for which there may or may not be evidence.

TB: What about the use of imipramine in panic disorder?

PL: Why has imipramine never been approved for the treatment of panic? Clearly, it was one of the drugs that Klein recognized had an effect in panic. It probably does work. Well, no one ever assembled the information and brought it to us and that is simply the reason. We don't go out and tell people that they should ask for approval of something. They have to actively seek something from us as an agency, and I think that's not well understood. Now we might or might not be willing to approve it, depending on the quality of evidence. There are a lot of things that are widely used on the basis of belief, for which no one can adduce evidence. In fact, I know of drugs that have been around for 10 or 15 years, widely marketed throughout the world, and I know the sponsors have tried to produce the evidence that show they work and they are unable to. A lot of physicians believe some of those drugs work. Now, until we see the evidence, I won't know, but it always dawns on me that there are many reasons why drugs appear to work. It's the old joke: use the new drug fast before it loses its power to heal. Another is, treat people very soon before they get better spontaneously. It's a combination of those two things. I don't know what accounts for it. But a lot of illnesses, for example, people with mild depression, do get better. The power of the FDA is to control the initial marketing of the product. The power is, therefore, to control labeling. The power is to try to keep the sponsor within the framework of labeling. They can't go beyond it, even if the drug is widely used. Now you can argue, that is a disservice to the community as a whole. You can also argue that if the firm wants to develop a claim beyond the one they have, they can collect the evidence, as required, and allow, therefore, for the regular scientific basis for which the drug works, rather than simply the observations of physicians. But there is this leak and it might happen that the drug will come on the market for a particular application and get used more broadly by people.

TB: But what would happen in case of a cardiac death of a patient treated for panic with imipramine?

PL: Then, if you go to court, if you're a professor, you could probably say, I do it because of my experience. If you're not, you could say there is a whole body of literature supporting the use.

You could probably point out in a court of law, where you're defending yourself for malpractice that I, with the informed consent of the patient, decided to use it because the patient could not tolerate alprazolam and now we've had this misadventure. It didn't turn out the way we wanted. People have this odd kind of belief that the FDA has control access to the market but all sorts of things get onto the market by other routes. There really is a body of information that hasn't been presented to the FDA in the form of a formal supplement seeking a claim; a marketer of imipramine might say, well, the drug is long since out of patent and there are generic forms available. Although we'd be willing to do it, they might see no economic gain in it. That still wouldn't prevent any practitioner from assembling the literature that supports the use, and say, here, it's perfectly reasonable to use it. Now, I realize that people and the legal system uses DSM-IV diagnoses and the FDA is hardly the final arbitrator of what good practice is. There are a lot of odd things going on because third party payers want to be able to spend less, and that they will disallow expenditures for uses they feel are outside what we've approved, and the agency is taking a very definite stand that its approvals speak to what the drug can be marketed and advertised for. The physicians are free to do what they feel is best practice, and we could go round on this forever; I think there's even been pressure to try and get people to submit supplements so that we can approve drugs for additional uses, if there's evidence, but it often turns out the evidence isn't very good. I think the agency ran into this when it did its drug efficacy review right after the passage of the 1962 amendments that were created as a basis for demanding proof of efficacy.

TB: Could you elaborate for us on the '62 amendment that led to the withdrawal of many drugs?

PL: There were thousands of products on the market but when they got finished, there were only hundreds. So many of them were marketed and there was no evidence and no one could produce any, so a lot of the drugs we had for treating dementia or dementia surrogates, or the treatment of depression, were banished. It doesn't mean they didn't work by the way; it's that no one was able to produce the evidence that met a minimum standard. You could argue that an armamentarium was better if you could have anything you want. I think that's good up to a point. If nothing works, it's fine to have a lot of products, which are not dangerous but then if one drug works, you could make the case that having anything in there that doesn't work, eludes the armamentarium and is a threat, as it might be with an antibiotic that didn't work. But clearly, these are the issues people are struggling with right now. How do you get efficient evaluation of drugs? How can you do it

according to standards? For example, if we were suddenly to lower the standards for proof for secondary claims, what impact would that have on the whole structure? You do need more than one. This is the other buffer. Anyway, I mean, clearly we aren't going to solve this particular problem because the one of standards is constantly undergoing review. In one breath, you want to be very sure that you know, not only that drugs are effective that we market, but we have been striving to find the conditions under which they should be used, find the differential risks in using them in subgroups of the population.

TB: Wouldn't you think that doing things in a standardized way, as for example using the Hamilton Depression Scale exclusively, in all studies, might have drawbacks?

PL: We haven't found ways around that. If you use the Hamilton Rating Scale for Depression only, you can argue that certain types of antidepressants come up and others don't, and then companies dump a whole lot of extremely useful drugs because they are not going to come out superior to the older drugs on the Hamilton Rating Scale. And if they don't come out superior, there's not going to be the marketing angle on them, and the return won't be there. Some of the newer serotonin reuptake inhibitors may, in fact, look bad on the Hamilton. So we don't care.

We've never said you can't approve the drug because they don't look good on the Hamilton Depression Scale. There is the Montgomery-Asberg scale and you can use that. If you come along with a new methodology that is untried and you're willing to take a chance, go ahead and take it.

TB: What about guidelines for industry?

PL: We've been encouraged to do that over the last decade, maybe because, people have argued that what the FDA wants is a moving target. So they wanted guidelines that tell them precisely what we will demand. Well guidelines are constricting. But Frank Young, who was Commissioner of the Food and Drug Administration, was under great pressure in the aftermath of the Sommer's Report, in 1986, and said, go out and create guidelines so that we'll be able to tell them at the industry level, in advance, what we're willing to accept as the minimum requirement. So, in the process of consensus building, we built guidelines, talked to a lot of people, had many sessions, and ended up with guidelines. I think if we had a drug that really stopped, for example dementia, we wouldn't need a guideline. But the industry demanded guidelines because they wanted more economic certainty. So a lot of the stuff isn't because I'm not able to tell if a drug works or not, but it's the question of what the industry wants. They'd like standards for showing that their drugs

are better than other drugs because it isn't just enough to believe your drug is better than another drug; you have to show it. There's going to have to be some basis to promote a new drug and advertise it.

TB: But insofar as I know, you don't have guidelines for that.

PL: Our law isn't a comparative law. We are not normally engaged in assessing whether or not you're better than another drug, only whether or not you do what the labeling claims you do. No doubt industry would like it. Should we have guidelines for comparisons? How would you choose the comparison drug?

TB: So, it seems that there would be difficulties in providing acceptable guidelines for comparison studies, and for the time being, we are stuck with placebo-controlled studies. As you know, there are some objections of requiring placebo control.

PL: Well industry does not want it because they are worried that the size of the treatment effects seen in most antidepressant trials is so small.

TB: Yes, indeed.

PL: Oh, I think it is getting smaller, that's why they don't want the added treatment. I mean ideally, everyone could be on cognitive treatment and the new drug should be an add-on.

TB: There might be also some other reasons why there are objections against the use of placebo.

PL: People don't like placebo because I think it requires you to take the patient who is ill and suffering and put them on a treatment that the investigator or physician knows, is unlikely to do very much. It may not do much harm but is unlikely to do very much good. If you believe there are active treatments out there, how can you possibly deny them access to an active treatment? Well that's fine if you knew your new drug really works, but if you don't know your new drug really works, to me it's incoherent that you would be willing to put them on this new drug that not only may not work, but also be dangerous and deprive them of access to the standard treatment.

TB: How do you get around that?

PL: Well, if you say the standard treatment doesn't always work, and we know that's true in 30 to 40% of people, you want to put a patient on placebo because you want to find out whether the drug you are working with works.

TB: In the old days we did open, uncontrolled clinical trials to see whether a drug works and then small single center controlled studies, but today, partly as a result of guidelines like the FDA's,

we have this large multi-center placebo controlled studies, in which all data is owned by the drug companies, and the individual investigators have lost control over their own contribution to the data pool.

PB: Well that probably has to be worked out by the investigators in the trial that make their agreements with the firms. I'm sure that there are examples of where firms haven't behaved in the best interest of the public, as for example, by not publishing negative results. But I suppose academic investigators are no less likely to publish negative results than are firms. Maybe we ought to publish all results of all trials. But, again, I think all of this is a question of looking at too few of the facets of a very complicated process. If you're going to develop new drugs, you have to ask who's going to do it. Since governments aren't going to do it, the private sector is going to have to do it. If the private sector is going to do it, why would they do it? I'm always struck by the fact there is a group that likes to think the FDA is a dupe of industry and fails to acknowledge that we wouldn't have any drugs if it were not for industry. It's the nature of how we've allowed our society to develop a drug industry. We didn't say the federal government is responsible for developing drugs, or the state government, or some costly public institution. We said we're going to let the laissez faire system work. People will come forward because of opportunity to make some degree of profit. It's true, we may make sure they don't make an egregiously excessive profit, but basically, it has to be driven by the profit motive. If that's true, industry cannot be seen as the devil and all bad. That doesn't mean that there aren't bad people in industry, and it doesn't mean that at times industry doesn't do bad things, but basically, that's where our drugs are coming from. Now the other side of the argument, of course, is that industry relies on government, that all this really comes from investigators, who were trained at universities, supported by the public. These people, as soon they get trained, run off to industry, and industry is reaping too large a profit. Well those are all political questions. Is the drug industry a utility? Is it a natural treasure? We never missed the merchant marine and our merchant fleet so much until we had to move all the troops to Saudi Arabia and then realized we had no sea lift capacity. You can almost argue that the private enterprise of industry is a valuable societal asset, and you need to support them, too. I'm not saying you need to give them rewards that they don't deserve but they can't be cast aside. They need you. You need them. This is not a conflict of interest, but rather a congruence of interest of a lot of different groups; and that's why you need to help them do placebo control trials, because we all

need to know whether a drug works. And without the industry having the resources to pay for it, there would be no controlled trials, no randomization, and drug development that meets current standards. I don't know how else you could do that. Academicians don't have the resources to produce the evidence that would be persuasive.

TB: So, you believe that without industry we would not have clinical drug development with our current standards.

PL: I've listened to Don Klein say many times, give me a drug, and I'll tell you whether it works. Well, I'm not so sure he can tell me in a way that I can hear. He may tell me he believes it works. He may, in fact, be right, but we're unable to listen to him, unless he presents it in a form where we can know in a public way if a drug works, and that's where the confusion is. I don't see there's any reason why, in the midst of a control trial that uses placebo, the astute investigator, if they are so prescient and confident, couldn't tell the difference. Why is placebo so confusing to them? Why has the structure of the randomized control trial so undercut their ability to pay attention to patients? I don't think there ought to be a patient who left a controlled study without the equivalent of a narrative summary of that patient, written by the PI, not his residents, not his clerks, not his co-PI's, not his nursing assistants, but by that PI, who says I saw Mrs. Jones, admitted three or four nights ago, or whatever, and she presented with these phenomena; I've treated her for six weeks and these are the things I saw and these are the things I didn't; I think she has improved. I can't, of course, know whether she was on a drug or not. I suspect she was on a drug because she had these things. These are the adverse effects she had. I think she did moderately well and sign his name or her name. We don't have that. I'd love to get that kind of a narrative summary on all patients, even if there are thousands of them. I can't see where the structure of the design would interfere with every clinician doing this.

TB: It certainly should not. What do you think the reason is that we got into this situation?

PL: If you really want to know what I think, it is that the guys who're talking about not being able to get done their work in the clinic or not being able to get to the bench, are the same people who are going to so many international meetings like these that they are on the tour and they don't have time to see anybody. I mean, I doubt whether they follow a patient. Patients need to be seen every day, don't they, or every week, depending on how sick they are, and I don't think they're doing it. They are not in town. I don't really believe that the modern trial prevents people from being astute.

Maybe the day and age does. Maybe everyone's life is so busy that they can't really see their patients and talk to them. It really doesn't make sense.

TB: Who is then doing the clinical trials?

PL: That's another thing. A lot of famous people put together consortia and they don't do the work. They take credit for the work.

TB: Does not NIH also create consortia?

PL: NIH has consortia of Alzheimer's groups they're supporting. They've not always had an Alzheimer's drug to run through it. But I think we do need clinical trial units standing everywhere ready to go, when we need to them. And because you need big trials and want them done fast, you probably can't rely on individuals being able to assemble them. I also think there's a great pressure for people not to have to go the physicians to get something they can treat themselves with.

TB: What are your thoughts about that?

PL: As you move toward that, there are greater risks. I'm struck with this with sumatriptan for the treatment of migraine. There are reports that some people, who have taken sumatriptan, died of subarachnoid hemorrhage. Would that be better if a physician would have prescribed it to them than if they gave it to themselves? That's a societal call. I don't know if I'd want to treat my own depression. I certainly wouldn't want to treat my own psychotic episode or my organic illness. But, I think what you find now is that in modern medicine, you can't reach your physician. My daughter has an acute disk right now, and I'm the one who has ended up treating her for her pain because of her inability to deal with a neurologist to get pain medication. It's unnerving how difficult it was, and I can imagine anyone with any kind of story of distress has the same problem.

TB: Could you tell us something about your recent activities at the FDA?

PL: I'm struck now with this paper that came out in the *New England Journal of Medicine*, an epidemiological study of the risk of connective disease in women who had silicone breast implants around Rochester, Minnesota, where the Mayo is. They always do a lot on epidemiology and in this study, they found there were increased risks. So, the *Wall Street Journal* writes an editorial about how crazy the FDA was and Kessler, in particular, was making this multimillion dollar decision, which paternalistically had prevented women who didn't have breast cancer but wanted to have access to these things on the basis of information, which turns out to be untrue. Well they

got it wrong. Kessler's position may have been paternalistic, I don't know, but there was no information. This is the first information that's really come out.

TB: What do you do in the absence of information?

PL: The view they espouse, at any time, represents a political viewpoint. I'm sure the guy who writes the *Wall Street Journal* editorials has his position about it. He'll latch onto anything he needs to make that point. This was a convenient one. It's not fair, but it's an example of how it goes now. If we had real knowledge of exposure of all products, we might be able to decide that for some individuals this or that drug has a relatively bad risk, and all I would do in that case describe that in the label. I wouldn't keep drugs off the market, if the drug works; this has been our philosophy for a long time and it seems to have a reasonable risk factor, but you probably want it out there.

TB: On this note, we should conclude this interview with Paul Leber. Thank you, Paul, for sharing this information with us.

44. WILLIAM T. MCKINNEY

TB: This is an interview with Dr. William McKinney⁴⁶ for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Tell us where and when you were born, about your early interests, education, and how you got involved in neuropsychopharmacology.

WM: I was born September 20, 1937, in Rome, a small town in Georgia, where I grew up and attended high school. I was an only child, my father was the town fire chief and my mother was a housewife. Not many people in my family had gone beyond high school but my parents had wanted me to and saved money for it. They were of modest means; my father built houses as an investment and then sold them to raise the money for me to attend college. I went to Baylor University in Waco, Texas. I think the reason I chose Baylor is that I was reared in a fairly religious background in the Southern Baptist Church and it was the largest Baptist College that existed at that time and may still be the largest. The idea of going to Texas appealed to me. My undergraduate major was in Psychology and English. Baylor had a very strong English department and I got very interested in writing. I had no idea that I might go to medical school when I started college; my family probably expected me to be a minister. But, when I got to college, my interests broadened quite a bit. I also loved psychology from day one. In the Abnormal Psychology course, my teacher brought in a psychiatrist as a visiting professor. I don't remember the man's name but what he had to say was exciting. He talked about the brain and, even though this was in the 1950's, how behavior could be related to biological factors. I began to think I might want to be a psychiatrist but to become one, I would have to go to medical school. I had no science courses in my junior year, so I had to catch up in order to meet the medical school entrance requirements. The last part of my junior year, the following summer and all my senior year was biological science. I took a year's worth of chemistry that Harvard put on in the summer. I don't think I could have abided it

⁴⁶ William McKinney was born in Rome, Georgia in 1937. After graduating from Vanderbilt University School of Medicine in Nashville, Tennessee he completed his internship at Bowman Gray Medical School, in Winston Salem, North Carolina and his residency training in psychiatry at University of North Carolina at Chapel Hill and Stanford University. He trained in the Intramural Research Program of the National Institute of Mental Health in Bethesda, Maryland, and then, joined the faculty of the University of Wisconsin in Madison. He subsequently became a member of the faculty of Northwestern University in Evanston, Illinois. He was interviewed in Waikoloa, Hawaii on December 10, 2001.

for a whole year. I completed all the requirements in my senior year and applied to medical school so that I could become a psychiatrist.

TB: It seems the psychiatrist your teacher brought in as visiting professor had a great impact on your future, even though you don't remember his name?

WM: I don't. But I do recall he was from a private practice setting in the area.

TB: So he was a practicing psychiatrist?

WM: He talked to us about the patients he saw and what his work was like. I was totally taken by it. At the time I applied to medical school, I had completed very few biological science courses and was still in the middle of catching up. I didn't want to wait another whole year, so I took the Medical College Admissions Test, and my scores were widely split, not surprisingly. They were very high in the verbal part and low in biological science. Some medical schools wanted to know more about me and others would look at the numbers and decide "No way." I was accepted and turned down by some very good medical schools but ended up deciding to go to Vanderbilt, which is only a few hours from my home town. There were just fifty-two students in our entering class.

TB: What year was that?

WM: I graduated from college in 1959 and started medical school that fall and graduated in 1963. During medical school, I changed my mind a few times about what I wanted to do, but I think there was a guiding stream throughout. I found myself migrating to psychiatric journals in the library, when I had spare time. I enjoyed a lot other things and came very close to going into neurology. There was a superb neurology teacher at the time, Charles Wells. He was head of neurology, when I was a medical student, and we wrote a paper together.

TB: What was it on?

WM: It was a historical paper about the Civil War, Weir Mitchell and neurasthenia.

TB: So, you did your first paper with Charles Wells on neurasthenia?

WM: I did my residency from 1964 to 1966 in Chapel Hill, and during that time, Charles decided to go into psychiatry himself and moved to do his psychiatry residency at Duke.

TB: At the time you did your paper with Charles, who was the chairman of psychiatry at Vanderbilt?

WM: William Orr. He was very influential and a wonderful teacher, who taught the first two year courses, although, in the second year, we also had small groups in which we started to learn psychopathology and the different syndromes, taught by Frank Luton.

TB: Frank Luton, a great man.

WM: A wonderful teacher. I had great teachers in psychiatry and neurology, throughout my medical student time. Frank Luton, William Orr, and Charles Wells, were on the front lines in terms of teaching and available to talk to us as students.

TB: Did you stay in contact with Charles Wells?

WM: We kept in touch.

TB: Are you still in contact with him?

WM: Not now, it's been awhile. But we've kept in touch over the years.

TB: What about Frank Luton?

WM: My memories of Frank are of sitting around a table with him in the conference room, going through the different syndromes and interviewing patients. We'd see people with different types of disorders and he was a very wise, wonderful man. It was a very positive experience to be exposed to him and to Bill Orr. Later, it was a real privilege to be asked by Mike Ebert to come back to Vanderbilt to give the first William Orr memorial lecture. I don't know how he got anything done in administration because he was always there for us and always very warm and interested. He was just a fascinating man.

TB: So you were taught psychodynamic psychiatry. Bill Orr was a psychodynamically oriented psychiatrist. Frank Luton was trained at Hopkins by Adolf Meyer.

WM: Yes, and we learned Adolph Meyer's way of thinking about psychopathology, early on. Charting life events and integrating those with temperament and genetic traits. Some of the things we now think of as new, Frank Luton was teaching me when I was a medical student. I'll never forget the first patient in my clinical psychiatry rotation. I was out at Central State Hospital, near Nashville. He had catatonic schizophrenia of the kind where the patient didn't move, didn't talk, and was mute. Frank and Bill Orr taught us to respect the patient's need for distance and predictability. You're respectful, not too demanding, but just there. They've got their space and you don't encroach on it. I would ask him if he wanted to talk or say anything but I wouldn't push too hard. I would just show my interest and might be there ten minutes or go away and come back

another day. Weeks passed and he didn't say a thing. Finally, toward the end, the patient started to talk. I'll never forget that.

TB: That was a great experience.

WM: And, internal medicine was taught well, too. Grant Willow was my endocrinology teacher. He was a great lecturer, very clear and a cutting edge clinician. I graduated there, in 1963, and had made the decision to go into psychiatry, but in 1963, one had to do a twelve months internship in something else. So, I did a full twelve months in internal medicine, a specialty I liked as a student. I did that at Bowman Gray Medical School, in Winston Salem, and that was a good year. It was my first experience having front line responsibility for patient care.

It was just about the time that they were stopping to do insulin therapy.

TB: Were they using modified insulin?

WM: No, the deep coma. They were doing it when I was an intern. We looked after also some of the patients when they were given sub-coma insulin.

TB: Was this in the mid-sixties?

WM: July of 1963 through June of 1964.

TB: For what indication did they use it?

WM: For some forms of anxiety, and some forms of schizophrenia.

TB: Insulin coma therapy for schizophrenia was lingering on.

WM: In July of 1964, I started my psychiatry residency at the University of North Carolina, in Chapel Hill. During my senior year in medical school, I had some elective time, and I spent it with Art Prange, at Chapel Hill. I did my first research project with Art. Morey Lipton was still there.

TB: What did you study with them?

WM: We published a paper called, "The Achilles Reflex in an Unselected Psychiatric Population."

TB: That's interesting.

WM: Art was getting interested in the thyroid, and one measure of thyroid function was the Achilles Reflex. You tapped a person's ankle and it had to break, a beam of light. The reflex was recorded on paper, which measured the time it took. We found that in a non-selected group of inpatients, those who were suffering from depression tended to have slower ankle reflexes, as a group.

TB: So, you found that depressed patients had slower ankle reflexes?

WM: Yes. There was another experience I had as a medical student that was relevant to my subsequent career. I spent a summer, between my sophomore and junior year, working in the Preventive Medicine Public Health Department, as an apprentice with a bio-statistician. He was doing consultations with faculty members on the design of their projects. When the study was done, they would do the data analysis. That was wonderful training in design and methodology issues.

TB: Both these research experiences as a medical student provided the groundwork for your residency.

WM: Yes. In 1964, Chapel Hill was a very active place with a lot of good faculty and residents, whose names you'd probably recognize, in the field.

TB: Can you name some of them?

WM: In my class were, Fred Goodwin, Bruce Green, Peter Whybrow, Lynn Dailey, David Markot, and Ali Jahre, who was from Saudi Arabia. I'm leaving two or three out, but I can picture them.

TB: That's fine.

WM: And a year ahead of us was Wyatt McCurdy, Albert Allen Wood, and Joe Mandels, all I think, active in psychopharmacology.

TB: Was Morey Lipton the Chairman of the department?

WM: Morey was a senior research faculty member; the Chairman was George Hamm. George Hamm had come from Chicago to start the department at Chapel Hill. George was a psychoanalyst and brought some other people with him. They had a series of acting Chairs during the time I was a resident. Morey was running and helping the research programs in the department. He was very important in my development, as good an advisor and senior mentor was Art. As a resident, I knew early on I wanted to do combined clinical and animal research and they really helped me do both for two years, before I transferred to Stanford for my third year because I wanted to see a different part of the country while I was single. I didn't leave out of dissatisfaction but for personal reasons. Stanford was very good; David Hamburg was Chair and a lot was going on there. In 1966-1967, I did my third year of residency and met my wife. We were married, in 1967, and have been married ever since. That was a good year. California was like a whole new world for me and

I remember a number of things about that year. A lot of people associated Stanford with research at that time, and that was true. They had good clinicians and researchers. I was able to arrange a consultation with David Hamburg about career development. He seemed very glad to meet and talk with me and advised me about a variety of issues. I finished my residency and, up to this moment, I had not done any primate research.

TB: What did you do after your residency?

WM: That's when I went to NIH for two years, and from 1967 to 1969, I was at the National Institute of Health, and worked part-time with William Bunney, who was branch chief. It was a very exciting time, because they started to use the new rating scales on their inpatients on the ward. This whole concept of doing clinical research and the way they were doing it, in a controlled setting, was very exciting. Biff Bunney put me on to the path of depression research, but I didn't quite know what aspect, until he suggested the animal models of depression. He had not published in that area and was too busy with other things to tackle it. There were a number of things in the literature that had never been brought to bear in an explicit way on this topic. One of the people whose work I was very interested in was Harry Harlow. I had known about his work as an undergraduate psychology student, so I wrote and asked if I could have some of his time. He was president of the American Psychological Association, with a long series of honors, but he wrote me a very thoughtful letter about the directions I might think about, including primate work. I began thinking that's the direction I want to go into and learn how to do animal research. Meanwhile, at Bethesda, I ran into Doug Bowden, who was in the Institute of Neurological Diseases, and had a primate laboratory. So, he and I started to do my first real primate project at NIH in the intramural program. That was a study in which we looked at the separation responses of rhesus monkeys with different types of frontal lobe lesions, compared to intact animals, and found that they were much more sensitive to the separation with more dramatic effects that lingered longer. It was an interesting project. In the Public Health Service, during those two years in Washington, I was also working in the Psychiatry Training Branch in Bethesda, involved in NIMH training grant review committees.

TB: When did you move to Wisconsin?

WM: I went to Wisconsin to work in the Primate Center and joined the faculty, in July 1969. I could have gone to a couple of other places that had primate centers, but I found the psychiatry

department in Wisconsin very different and interesting. The Chair was Milton Miller. I like Milt a lot. He's a very caring person and thoughtful administrator. It's a nice combination. It was also a very strong clinical psychiatry department at that time. All of all that, with the primate center and Harry Harlow being there, was what attracted me. I also liked Madison, the town, so I wound up there. When I started, the primate center lab didn't have an office for a psychiatrist, so Harry, this world famous psychologist, invited this brand new faculty member to share his big office. I shared it for maybe a year or so. Harry was always prey to people, coming in to talk to him, but it was very rarely that he asked me to leave. That was a real growth experience.

TB: So your interest in primate work started while working with Biff Bunney looking for animal models of depression?

WM: Yes, absolutely. I knew I was interested in some type of depression research. When I got to NIH, after finishing my residency, Biff challenged and stimulated me to look for animal models and to think about opening that up as a research area. He deserves full credit for that. He and I wrote one of the first papers called, "Animal Models of Depression," in which we charted out some of the criteria and how to go about developing models, and criteria for evaluating them. He and I wrote that article around 1969, and I think it was published in the *Archives*. Biff stimulated me in the general area of animal models and Harry provided me an infrastructure and a setting, in which I could learn to do primate research, and think about behavior in a developmental sense. Harry was interested in building on the work he had done over many years, starting first with learning, based on the cognitive work developed with the Wisconsin General Testing Apparatus. From there we went to the relevant social attachment systems, to disruption of attachment systems and then to separation studies. He was interested in extending it into biological areas, but it wasn't quite his thing to link it up with psychopathology. So, the timing was good, because I was able to help him with that and he certainly helped me in providing an infrastructure in terms of learning how to do primate research. There was a lot going on there at the time and it was a very exciting place to be.

TB: Are we now in the mid-1970s?

WM: I arrived at Wisconsin, in 1969, and over the first five or six years we got my primate research program going.

TB: Could you say something about the primate research you did?

WM: I had to learn the techniques of doing primate research, how to develop and utilize different types of rating scales, how to work with the animals, and what kind of biological and drug studies one could do in primates. I also had to think through where primates fit in the spectrum of different approaches. I'd been intrigued early on by the literature that was starting to emerge about the role of early experience in shaping behavior and influencing neurobiological development, across the life span. It was in Harlow's group that some of the findings in this area of research came from. There are four or five other people who have documented effects of early isolation on biological and behavioral development. I was interested in that, so that's an area I started with. We worked with animals that had been socially deprived and then tried to find ways to reverse it. We tried chlorpromazine in some monkeys and it reduced the large array of abnormal behaviors they displayed. When we stopped the medication abnormal behaviors came back. We didn't have a variety of different neuroleptic agents as we have now to study. Later on we tried antidepressants in some of the separation paradigms, too.

TB: Which paradigm did you work with?

WM: I was working with the isolation and the separation paradigm.

TB: So, you worked with both paradigms?

WM: Yes. In the isolation paradigm, we were involved in studies showing that a neuroleptic was effective in reversing all the abnormal behaviors; benzodiazepines were not.

TB: So the reversal worked with chlorpromazine?

WM: It did.

TB: Could you see the effects of separation on individual monkeys?

WM: Not individually. If you make social isolation severe enough, you start to minimize the variation, although you don't do away with it. The more severe you make it, the less individual variation there will be. Just like an extremely traumatic event.

TB: What would chlorpromazine actually do?

WM: It would reduce a lot of the abnormal behaviors that the animals would show as a result of the early experience. We also found, in collaboration with Harlow, that you could treat these animals by providing them social experience with younger peers. We did more recent work through the MacArthur Foundation, showing how early experience got effects in a lot of domains, including neuroanatomical changes. We did this later work in collaboration with a group in New

York, at Mount Sinai, involving John Morrison and Steve Siegel. We demonstrated for the first time that early isolation experiences could have significant cytoarchitectural effects in the hippocampus. I don't think many people knew quite what to make of that but the finding was solid and clear. Subsequent work in a variety of early stress paradigms has replicated and expanded this initial finding. In collaboration with Gary Kramer, a student in my group, we demonstrated that if you took socially isolated animals and rehabilitated them so they looked normal, and then you challenged them with a low dose amphetamine, they were hypersensitive to it, as opposed to animals that had not been in social isolation. They became hyper aggressive; even lethally hyper-aggressive. So the early experience was only seemingly reversed. They were carrying scars of vulnerability, based on their early experience, and if you challenged it, you could bring it out. Finally, maybe I'll talk about the separation paradigm. Harlow and two or three other labs had already shown that by separating rhesus monkeys from their mother, you get a biphasic protest-despair response, which show significant similarities to descriptions of human infants. I did a series of studies focusing on the pharmacological aspects. I studied imipramine first and it worked. If it doesn't work right away, you had to take them through a couple of cycles, but imipramine can block the separation response. We've recently shown that fluoxetine does the same thing. Antianxiety drugs can influence the initial response but don't block the total depressive responses that occur after separation.

TB: Did you try desipramine?

WM: We did do desipramine.

TB: What about MAOIs?

WM: That's a good question. We don't know whether an MAOI would do it or not.

TB: What about meprobamate?

WM: Meprobamate has not been tried, to my knowledge.

TB: What about diazepam?

WM: It doesn't work. The studies take a while to do, they're not so simple.

TB: You started to work with the separation model, in the 1970's, and are still using it?

WM: Yes. In 1993, I moved to Northwestern to start a research and treatment center. I wasn't really looking to move, but this was a good opportunity.

TB: Before moving onto that, am I correct that you were at a certain point Chairman of the Department of Psychiatry at the University of Wisconsin. When was that?

WM: I was department Chair from 1975 to 1980.

TB: But, even while you were chairman, you continued your research?

WM: Yes. I liked being Chair and did not dislike the administration. I didn't leave it for that reason, but realized I couldn't do everything, and decided to focus on research, teaching, and clinical work. I had accepted a Dow Chair at Northwestern to start this Center. It was a new challenge.

TB: Could you say something about the Center?

WM: The overall charge is to be multidisciplinary, dedicated to understanding the diagnosis and treatment of depressive disorders. We have a basic division and a clinical division and the basic division is heavily oriented toward behavioral neurosciences. We have four or five basic neuroscientists in the basic science division, a clinical mood disorder program with five psychiatrists involved, and an administrative person. We have a small primate operation focused on circadian biology issues. I'm collaborating with a neuropharmacologist, Dr. Dubocovich, and there's also a strong circadian biology group on the Evanston Campus, looking at melatonin receptors.

TB: So you are looking at melatonin receptors?

WM: Collaborating with the neuropharmacologist, looking at melatonin receptor subtypes she has characterized in other species. She's looking at different agonists and antagonists through the different melatonin receptor subtypes and characterizing the effects they have on circadian biology disturbances in primates. Three or four people at the basic science level are looking at different types of gene expression and working at the molecular neuroscience level. The Center ranges from scientists working at the molecular neuroscience level to clinicians doing clinical trials.

TB: Do you have an outpatient clinic to treat patients?

WM: Primarily outpatients, although people in the program will work on the inpatient service, if patients need to be hospitalized.

TB: Do you have a certain number of hospital beds?

WM: The department has its own service and we can admit someone as long as they're beds available.

TB: Are you having both unipolar and bipolar patients?

WM: It not designated bipolar and unipolar; it's defined as mood disorders.

TB: Mood disorders?

WM: We see bipolar and unipolar patients and people with major comorbidities. We are not an anxiety disorders program, but anxiety disorders comorbid with depressive disorders are fine.

We also see people with substance abuse problems and mood disorders.

TB: Could you say something about the ongoing clinical research in the center?

WM: I'd have to add them up. We're one of the regional centers for the STAR D study. We're also a regional center for the KD schizophrenia and KD Alzheimer's studies. We're involved in the TADS, adolescent depression project, with a psychologist named Mark Reineke, who is the Principal Investigator (PI). We are one of the sites for ancillary studies from STAR D to Child STAR D.

TB: Can you tell us what STAR D means and something about the study?

WM: STAR D means Sequenced Treatment Alternatives to Relieve Depression and this is an NIH funded, multi-site study, with John Rush and Madhukar Trivedi, as PIs, at the University of Texas. There are fourteen regional centers around the country, and we're one of those. One of the ancillary studies to that is a Child STAR D, and there are five or six centers in that study.

TB: So you are very active.

WM: Very active. It's been a good move; a new challenge at this phase of my life and I'm glad I did it.

TB: How much of your time is spent in clinical, how much in teaching, and how much in research?

WM: Probably a ten-hour day, seeing patients during a week. And then, of course, there are additions to that.

TB: So you spend at least one fifth of your time seeing patients?

WM: At least one fifth of my time seeing my own patients and I see other patients in the context of some of the studies and trials.

TB: How much teaching?

WM: Teaching varies. I teach a journal club to our residents and organize the neurobiology seminar series. I teach in that series, organize it, and get other neuroscientists from around the place to help teach the residents.

TB: How much time does that mean?

WM: Probably about half-time and about half-time. I've always felt strongly about maintaining my own patients.

TB: What would you consider your most important contribution?

WM: From a research standpoint, I think developing the concepts of animal models in the field of psychiatry and laying out the groundwork and framework for a series of studies that have since been expanded by others in a variety of different directions. It was really a major move in terms of opening up that whole area for the field. I've trained people over the years and I feel good about that.

TB: Would you like to name some of the people you trained?

WM: Hagop Akiskal was a resident of mine. Ned Kalin came to Wisconsin when I was on the faculty and did his first primate work with me. Akiskal came to me as a third year resident and transferred into our program to think through ways to approach research in depression. Akiskal has, obviously, blossomed. He's editor of the *Journal of Affective Disorders*; he just got the NARSAD Award this year in the Affective Disorders area. There's a number of clinicians I've been involved in training. They're in various practice settings, some academic and some private settings around Wisconsin, and I've watched the leadership roles they've taken over the years. I feel very good about that. Gary Kramer, a graduate student of mine, is now a tenured faculty member at Wisconsin. We trained a half dozen or so people who have gone on to various kinds of careers in the field. I feel good about one of our chief residents in Wisconsin, Randy Thompson, who is now down in Chicago heading up one of the major hospitals. I, also, feel good about the fact I have not stayed in the lab all the time. I've done other things. For example, I've been Director on the American Board of Psychiatry and Neurology for eight years and just finished up my rotation. That was a very time consuming job, but I felt strongly about staying active in the field of psychiatry. I, also, tried to keep a personal life through all this.

TB: Would you like to talk about that?

WM: I have other interest besides my work. There's absolutely no way I could have achieved what I have without the support of my wife Carolyn and my children, who tolerated a lot. The things I've described take a lot of time and travel. My family has been very supportive, so I feel really good about that. My son, Scott, who is twenty-nine, is married to Kristin and I have a

daughter, Julia, she's twenty-five, who lives and works in Houston. I've tried to keep my priorities straight over the years. I've got interested in running and I've become a runner. TB: A runner?

WM: Yes, not racing, just jogging and running. I've been running all my life. I think I've done eleven marathons now. I started that when I was fiftyish.

TB: That's great! What was your last paper?

WM: Gary Tucker called and asked me if I would edit a special issue of the journal that he's the overall editor in *Seminars in Neuropsychiatry*. He wanted to do a special issue on "Stress and Affective Disorders," and asked me if I would be the guest editor and write an article for it. I did the editing, rounding up everyone to write the papers, wrote an introduction and an article, myself, on "Stress, Animal Models and Depression."

TB: You have been involved with ACNP for approximately twenty years.

WM: A little bit more than that now.

TB: Have you served on any of the committees?

WM: I've been on committees. I've been active. The meetings are at a difficult time of the year, in terms of family life, and the things we value as a family. I've tried to come to meetings, but I've missed some. I'm on the education and training committee, now; I've been on the committee that deals with advocacy groups and I'm joining the animal committee, starting in 2002.

TB: Have you written any books?

WM: I've written two.

TB: What are they?

WM: One called *Animal Models in Mood Disorders* that I wrote myself and the other called, *Mood Disorders: Towards A New Psychobiology*, is written by me, Peter Whybrow, and Hagop Akiskal.

TB: When were they published?

WM: In the late eighties.

TB: Is there anything important we did not cover?

WM: As a junior faculty member, when I had a research career at NIMH, I was able to put together a sabbatical with Robert Hind in Cambridge, so that was really important. And, then, in the mid-eighties, I was a Fellow up at the Center for Advanced Behavioral Sciences at Stanford for a year, and that was also a very good, important year.

TB: Is there anything else you would like to add?

WM: I think this is a very exciting time for the field right now. So many new developments are going on. I would like to see basic and clinical developments, to see these domains stay in touch with each other. The areas are getting so specialized that to do it on an individual basis can be awfully hard. One person can no longer bridge this anymore. We've got to think through new ways for it to happen, for the interaction to occur. This is where I think the College has played an increasingly important role, because you've got in the same organization, clinician researchers and highly skilled basic neuroscience researchers. Things have changed so much that we've got to find other structures to help to do this.

TB: On this note we should conclude this interview. Thank you very much.

WM: Thank you.

45. CHARLES B. NEMEROFF

TB: We are at the 38th annual meeting of the American College of Neuropsychopharmacology at the Acapulco Princess, in Acapulco Mexico. It is December 1999, and I will be interviewing Dr. Charles Nemeroff.⁴⁷ I am Thomas Ban. Let's start from the very beginning. Could you tell us where and when you were born and something about your early interests and education?

CN: First, it is an honor to be interviewed for the ACNP archives. I was born, in 1949, and was brought up in the Bronx. I attended the New York City public schools and, in fact, like many of us in those years, had the opportunity to skip the eighth grade. In 1966, I graduated from George Washington High School in New York, which is the high school Rod Carew, the Hall of Fame baseball player attended. I then attended the City College of New York, like many of my heroes, including Julie Axelrod and one of my key mentors, Morrie Lipton, who I will talk to you about later. After attending the City College of New York, I moved to Boston, where I started working at McLean Hospital, in their research laboratories. This facility was obviously much smaller than it is today and I worked as a research assistant in the laboratory of Victor Shashoua, who at the time was studying neurochemical changes in the brains of goldfish after a new learning task, was accomplished.

TB: How did you get that job?

CN: I obtained that job because I had worked in the Department of Ichthyology at the American Museum of Natural History, in New York. I was supported by a small NSF grant, during my undergraduate years, in New York; this was my first exposure to research. With this experience in ichthyology, I got the job because there weren't very many people that knew how to handle goldfish. I was hired, in 1970, as a research assistant at McLean Hospital, a major teaching hospital for the Department of Psychiatry at Harvard Medical School. Once there, I started attending various research seminars. This was a very exciting time, and there were many, many, seminars.

⁴⁷ Charles B. Nemeroff was born in the Bronx, New York in 1949. He received his Ph.D. degree in neuroscience and then began medical school at University of North Carolina at Chapel Hill, where he also completed his residency in psychiatry and had his first faculty position. He became a member of the faculty of Duke University Medical Center, in Durham, North Carolina before moving to Emory University School of Medicine in Atlanta, Georgia. He was interviewed in Acapulco, Mexico on December 13, 1999.

TB: Could you tell us about the people who worked there at the time?

CN: The laboratory was directed by a very dynamic neurochemist, Jordi Folchi-Pi, who had come from Spain to the United States. There were a number of other investigators there, Harvey Shein, a psychiatrist, George Hauser and Joseph Eichman, neurochemists, and others. It was a very exciting time and I had the remarkable pleasure of meeting Alfred Pope, the head of neuropathology at McLean Hospital and a professor of pathology at Harvard. He had worked with Oliver Lowry in pioneering microchemical studies of the cerebral cortex. He, in fact, was the person who, with Oliver Lowry, had invented a quartz microbalance scale, so that he could actually weigh each layer of the cortex. And, what Alfred did, in those years, was to dissect each of the layers of the cortex and, then, measure, with very elegant techniques, various enzyme activities. This was really the beginning of modern quantitative neurochemistry. Alfred had no children; his wife was a psychiatrist at Massachusetts General Hospital. He took me under his wing and mentored me, almost as a surrogate child. I enrolled into the master's degree program at Northeastern University, in Boston. It was interesting. I applied to several graduate schools in the Boston area; the chairman of biology at Brandeis University, in Waltham, Massachusetts, said I would never amount to anything and that I should keep my research technicians job at McLean and not attempt to apply for any higher degree. I remember leaving his office rather crestfallen, but Alfred Pope continued to be enthusiastic about my graduate school and medical school training. Alfred Pope served as an adviser for my master's thesis and virtually every day after work, we would sit down and use the double-headed microscope in his office and go over the studies that I have been conducting on the blood-brain barrier for my master's thesis at Northeastern. These were studies that demonstrated that during seizures, the blood-brain barrier was reversibly opened, allowing proteins and other substances into the brain that normally wouldn't enter the brain. After I finished my master's degree, Alfred said to me, "you must get a Ph.D., and I think you should get a Ph.D. in neuroscience."

TB: Where did you get your Ph.D.?

CN: There were only three universities in the United States, in 1973 that offered neuroscience Ph.D. degrees that I was aware of, the University of Florida in Gainesville, the University of Illinois in Champaign Urbana, and the University of North Carolina at Chapel Hill. Having been brought up in New York City, I certainly did not want to live in cold weather. I ultimately ended

up deciding to go to Chapel Hill, where I almost immediately met two individuals that would irrevocably change my life: Morrie Lipton and Arthur Prange. Both of these individuals are past presidents of ACNP. The reason I ended up going to Chapel Hill, and not to a program I was accepted into at Duke, in Durham, North Carolina, was primarily because Duke had a double language requirement for the Ph.D. degree, and I knew that I would have had difficulty with that requirement.

TB: Could you tell us something about Morrie Lipton?

CN: Morrie was one of the most remarkable individuals I have ever met. He earned his Ph.D. degree in biochemistry from the University of Wisconsin and an M.D. degree from the University of Chicago. Both he and Art Prange were psychiatrists. One of Morrie's remarkable attributes was that he was as comfortable talking to the fellow that mopped the floor in the research building, where we worked, as he was talking to the Dean or the President of the University. He was truly egalitarian and that is something that has stuck with me and something that I have tried to emulate. At any rate, I ended up working with Art Prange for my Ph.D. degree.

TB: So you ended up working with Art.

CN: He was my doctoral mentor. My Ph.D. dissertation was on, "The Effects of Thyrotropin Releasing Hormone (TRH)." In those days, neuropeptides were just being discovered in the brain and no one believed that they had effects on the brain, other than endocrine effects mediated by their actions on the pituitary. I remember, time after time, our abstracts documenting CNS effects of peptides submitted to the Endocrine Society for presentation at their annual meeting were routinely turned down for presentation because their leadership did not believe that these peptides were really neurotransmitters. Art Prange was a fabulous role model, because he conducted both basic science research and conducted clinical research, a true translational scientist, and was a fabulous mentor. Part of being a good mentor is to know when students should be left alone and other times when they need direction; Art was very good at that, and he let me stumble around a bit as I progressed with my Ph.D. studies.

TB: When did you get your Ph.D.?

CN: I completed my Ph.D., in 1976, at the University of North Carolina at Chapel Hill. I applied for and was awarded a Fellowship stipend from the National Institute of Neurological Disorders and started to work in the laboratory of an internist-neuroscientist in order to begin to learn

molecular neurobiology, which was then an emerging area. My postdoctoral mentor was Steve Kizer, who had trained at NIMH with Julie Axelrod and Mike Brownstein. I spent a year working with Steve and I learned several things. First, it taught me that I didn't do well in a laboratory that had no windows and it taught me that I missed interacting with a large number of students and fellows. With Morrie Lipton and Art Prange's encouragement, I ended up applying for admission to the UNC medical school and I began as a medical student, in 1977. I graduated from medical school, in 1981, and then, began my internship and residency at UNC, where I met Dwight Evans, who is a member of the ACNP. Dwight, at the time, was a junior attending on the inpatient psychiatric service at UNC. Over the next four years, we probably published ten to fifteen papers together, largely studies of pituitary-adrenal and pituitary-thyroid axis abnormalities in patients with mood disorders.

TB: Didn't you work at Duke at a certain point in time?

CN: I was recruited to Duke University Medical Center with my colleague, Garth Bissette. This was an exciting time in neuroscience and psychiatry. Ranga Krishnan, Saul Schanberg, Ted Slokin, and Redford Williams were there, as was Clinton Kilts. I had a variety of graduate students in pharmacology who conducted their Ph.D. research in my laboratory including Mike Owens, who is a member of the ACNP, and Beth Levant, a faculty member at the University of Kansas, and a variety of other fellows and students. We stayed at Duke, from 1983 to 1991, and during those years our laboratory focused largely on neurotensin, a thirteen amino acid containing peptide that appears to be involved in the mechanism of action of antipsychotic drugs. We also began study of corticotropin-releasing factor (CRF), which was discovered in 1981. This forty-one amino acid-containing peptide that controls the pituitary-adrenal axis appears to be hypersecreted in depression and perhaps in certain anxiety disorders; CRF receptor antagonists are a novel class of antidepressants and anxiolytics that are currently being developed.

TB: When did you move to Atlanta?

CN: In 1991, a remarkable opportunity arose that was simply too exciting to pass up and that was the opportunity to relocate to Atlanta to Emory University where the Chairman of the Department of Psychiatry, Jeffrey Houpt, had become the Dean of the School of Medicine. With the sizeable development package provided to me by the university, we were able to recruit a number of talented new faculty, many in collaboration with other departments. These included Michael

Davis from Yale, a leading behavioral neuroscientist, Clinton Kilts from Duke, a PET imager and extraordinary analytic neurochemist, and Tom Insel from the NIH, who became Director of the Yerkes Primate Center and, then, eventually the Head of the NSF-funded Center of Behavioral Neuroscience. Jay Weiss, one of the leading investigators in animal models of depression, joined the department as did Michael J. Owens, my former graduate student and fellow, William McDonald, one of the leading investigators of ECT and now transcranial magnetic stimulation and head of medical student education, and Paul Plotsky from the Salk Institute. We have gone on to continue to recruit young M.D./Ph.D.'s and M.D.'s and in the almost nine years that I have been at Emory, the department has grown considerably in terms of its research portfolio. We have been able to receive generous support from philanthropic sources and substantially increase our NIH funding.

TB: What are you working on now?

CN: In recent years, I have focused largely on the long term neurobiological consequences of early trauma. As I am sure you know, we have an unacceptably high rate of child abuse and neglect, not only in the United States, but worldwide. We have also been conducting studies in laboratory animals, rodents, and non-human primates, as well as clinical studies, showing very long term consequences of maternal neglect. We believe that the consequences, which are changes in the activity of the HPA axis, changes in CRF gene expression, and changes in a variety of other neurotransmitter systems, underlie the vulnerability of these individuals to the development of mood and anxiety disorders. We are now beginning several treatment studies in this clinical population and my hope is that eventually we can begin to look at prophylactic treatment to prevent depression in this "at risk" group.

When I look back at the career that I have had, I have been lucky. I have been fortunate to have a fabulous family. I have had a fabulous team of colleagues, support staff, junior faculty, and perhaps, most importantly in relationship to this current interview is the remarkable friendships that I have made with ACNP members. These individuals, just to name a few, include Jack Gorman, Ned Kalin, David Rubinow, John Newcomer, Jeffrey Lieberman, Peter Kalivas, Dennis Charney, Marty Keller, Danny Weinberger, Dwight Evans, and Alan Schatzberg. They have become best friends to me and my family because we all travel a great deal to a variety of

meetings. This is one reason why the American College of Neuropsychopharmacology isn't just a professional society like the American Medical Association or the American Psychiatric Association. In contrast, the ACNP is a college, meaning that the individuals are collegial, and I could probably name twenty or thirty individuals, who I feel sufficiently close to in this College, that I could go to with any personal or professional problem that might arise, either, in my department or in my personal life. And, I believe that's why the ACNP means so much, to so many of us. Of all the organizations I belong to, and I have multiple affiliations with a variety of organizations, this is the organization I feel closest to, and I know that my colleagues would echo these sentiments as well. I was an ACNP travel awardee and became a member, though my membership application was rejected the first time I applied, a not unusual occurrence, as you know. Eventually I became a fellow, a member of the council, and was elected president. The ACNP is very important to me. And, not only have my relationships with members blossomed, but with their spouses and children as well. In life, it is not only the good work that we do, which hopefully translate into better care of the patients that we have spent so much time caring for over time, but also, the friendships we have, which, in fact, contributes a great deal to the quality of our lives. It is for that reason that so many individuals have put so much time and effort, without remuneration, into this college. We have lived through fabulous times here at the College and we witnessed tragedies. Morrie Lipton, one of my mentors, suffered a CVA at an ACNP meeting in Puerto Rico several years ago. I think of the ACNP, as a family, usually functional, but occasionally dysfunctional, with occasional squabbles among its members, as one would expect from a talented, intelligent, and strong-willed group of family members. There isn't any other organization that combines excellence in neuroscience, clinical psychopharmacology, epidemiology, genetics, molecular neurobiology, and brain imaging that this College does. It suits my needs because I can come to these meetings and learn about areas that I simply don't know enough about and try to take my own research to the next level. I don't know any other organization like this.

TB: Could I ask you a couple of questions about the research you are involved with in developing new drugs?

CN: OK.

TB: Could you elaborate on that area of activities in your research?

CN: By history, the development of new agents to treat major psychiatric illness has been an area that largely has been characterized as serendipitous. There have been many attempts at rational discovery in psychopharmacology, but in the end, most of the drugs that we have were truly serendipitous discoveries, including antipsychotics, monoamine oxidase inhibitors, and even the tricyclic antidepressants. Because of the elegant work of many members of the College that showed hyperactivity of the HPA axis in depression, the discovery of CRF in 1981, led to a series of studies to characterize whether CRF is, in fact, hyper secreted in depression. These studies, virtually unanimously, pointed to hypersecretion of CRF in depression and, not only that, but our and others' laboratory animal studies showed that when CRF was injected into the brains of these animals it produced the full constellation of what we see in patients with depression and certain anxiety disorders, including decreased libido, decreased appetite, and disrupted sleep. This work led to the development of CRF receptor antagonists as potential novel antidepressants and anxiolytics. Several pharmaceutical companies have, in fact, developed antagonists to the CRF₁ receptor that preclinically exhibit antidepressant and anxiolytic effects. The race is on to determine which company will be the first to demonstrate efficacy in clinical trials. If efficacy is demonstrated for CRF₁ receptor antagonists, then this will represent a new class of agent with a totally novel mechanism of action that may exhibit a broad spectrum of therapeutic activity ranging from post-traumatic stress disorder, to major depression, to a variety of other disorders, such as irritable bowel syndrome. These agents could even be used preoperatively instead of benzodiazepines to reduce anxiety. The other area that I would want to mention, in terms of drug development, is our work on neurotensin, a CNS neuropeptide that, in part, mediates the effects of antipsychotic drugs. Basically, what we have discovered is that typical antipsychotic drugs increase neurotensin gene expression and release in the striatum and that appears to predict extrapyramidal side effect liability, whereas atypical antipsychotics, the latter including olanzapine, risperidone, and quetiapine, increase neurotensin gene expression in the nucleus accumbens, but not in the striatum, and this predicts the clinical efficacy of antipsychotics. The question as to whether a neurotensin receptor agonist might represent a novel class of antipsychotic drug is a very hot avenue of investigation at the current time. No such molecules have yet been discovered.

TB: Simultaneously with your research, you have built a very successful department of psychiatry. So, you have administrative, teaching, and clinical responsibilities.

CN: Yes.

TB: It has to be a difficult task to deal with all the different responsibilities.

CN: I suppose so. We have about 110 faculty members in the Department of Psychiatry at Emory. Of all the departments at Emory, we are the second best funded department in terms of research. Obviously, a considerable administrative load is associated with running a large department. I have been blessed to have vice chairs that I clearly have to depend on and to whom I delegate tremendous responsibility. Steve Levy, the Chief of Psychiatry at Grady Hospital, is the Vice Chair for Academic and Clinical Affairs and Clinton Kilts, is the Vicechair for Research. Because I have a fabulous staff, as well as these vice chairs, I have been able to continue my research career and teaching as well. I currently have 3 M.D./Ph.D. students that I am mentoring, as well as a number of Fellows. I have a fair number of patients that I still follow, approximately eight to ten hours a week, largely with refractory mood disorders. Then, of course, I have the inevitable administrative responsibilities, including search committees, chair's meetings, and the like. Recently, I have had an increase in my interactions with the Carter Center, which is also part of Emory, and Mrs. Carter, of course, has a special interest in mental health. I would conclude by saying that one has to love these jobs in order to do them even reasonably well. I would never suggest that I was very good at all of these tasks but I can tell you that I have enjoyed them. You really have to love your faculty if you are willing to take on the often thankless task of the administrative responsibilities which enable the faculty to be successful. I think the job of the chair of the department is to work as quietly behind the scenes, as possible, in order to maximize the opportunities for the faculty to accomplish their goals; their clinical goals, their research goals and their teaching goals. If you can do that, without them knowing how precarious this house of cards is sometimes, then, I think you have accomplished your job. I have been very lucky in my life to have the support of great mentors and great students and great colleagues and a great family and would simply hope that all of you watching this video could be as lucky as I have been in the fifty years I have been on this earth, and hopefully, a little bit longer.

TB: During the years you have written many papers. Could you tell us something about your publications?

CN: I have published 600 peer reviewed journal articles, including reviews, many co-authored by my colleagues and junior faculty. The journals in which they are published range from the *Journal of Neuroscience* to *Science*, *Nature*, *Biological Psychiatry*, *Neuropsychopharmacology*, *Journal of Clinical Investigation*, and the *Proceedings of the National Academy of Sciences*. I have also had the pleasure of editing the *Textbook of Psychopharmacology* with Alan Schatzberg, currently president elect of ACNP and one of my closest friends. This week, the book that we authored together on psychopharmacology for non-psychiatrists, largely for primary care physicians, is about to be published. I have also edited about 12 other books in the areas of neuropeptides, neuroendocrinology, and psychoendocrinology. I think that of all of my publications, the *Textbook of Psychopharmacology* is, by far, my favorite, because it has performed a service for the field. This year, I will complete a four-volume *Encyclopedia of Psychology and Neuroscience* that Ed Craighead, a professor of psychology at the University of Colorado, and I are co-editing. This is formerly *Corsini's Encyclopedia* used largely by psychologists, which we have converted to an encyclopedia of psychology and neuroscience. I am also now working on a CD-ROM project on neuroscience in psychopharmacology for psychiatrists and other physicians, which I hope will be used as a teaching tool to educate about receptors, receptor subtypes, transporters, molecular biology, circuits, and cognate areas. I also write a column for the journal *CNS Spectrum* every other month on a topic of my choice, which has ranged from personal columns about tragedies in our lives to topics of professional interest.

TB: During the years you served on many advisory boards.

CN: Yes. I have served on a number of advisory boards in mood disorders and in schizophrenia. I have worked very hard to try to bring together the pharmaceutical companies and academic investigators to discuss investigations of novel clinical agents, and ethical concerns, such as placebo use in severe psychiatric disorders. I am currently the chair of the Scientific Advisory Board of the National Depressive and Manic Depressive Disorders Association, an advocacy group for patients with bipolar disorder and depression. I am the vice chair of the scientific advisory board of the Anxiety Disorders Association of America, led by Jerilyn Ross, a remarkable individual. Dennis Charney is currently the chair and I have worked closely with him in that organization. I have been involved with the National Alliance of the Mentally Ill (NAMI) and

with the Mental Health Association. I serve on a foundation board in Atlanta dedicated to the treatment of patients with mental illness, the George West Mental Health Foundation.

TB: What would you consider your most important contributions?

CN: I think I am probably as good a fisherman as anyone in the College and have tried to convert many ACNP members to fly fishermen. I'd rather be fly-fishing than probably doing anything else except for being with my family. Scientifically, the contributions we have made in the CRF field and the neuropeptide field in general, and, perhaps, some of our work in the serotonin transporter field will stand the test of time.

TB: You have trained many people. Would you like to mention some of them by name?

CN: I have had the chance of working with many superb junior colleagues. Beth Levant was my Ph.D. student, one of the world's experts on the D₃ receptor, and she is on the faculty of the Department of Pharmacology at the University of Kansas. Mike Owens, my first Ph.D. student is on the faculty at Emory and has gone on to conduct remarkable work on urocortin, the CRF₂ receptor, and their role in the mechanism of action of benzodiazepines. Jeff Newport, my former Fellow, is now a faculty member at Emory working with Zachary Stowe, another former fellow, on depression in pregnancy and in the puerperium. My junior colleagues have been absolutely terrific in contributing to my own work and then moving on to establish their own independent careers.

TB: So you trained quite a number of people who pursue, now independently, their own area of research and you have yourself opened up several new areas of research that will hopefully grow.

CN: Well, as you know, Tom, different scientists have different styles. Some work on one distinct area throughout their entire career. Others, like me, prefer to conduct research, make new findings, and then move on to other areas. Having diverse interests has really kept me going.

TB: On this note we should conclude this interview with Dr. Charles Nemeroff. Thank you for sharing all this information with us.

CN: Thank you, Tom

46. JOHN E. OVERALL

TB: This will be an interview with John Overall⁴⁸ for the archives of the American College of Neuropsychopharmacology. We are in New Orleans at the Annual Meeting of the American Psychiatric Association, in May 2001. I am Thomas Ban. I'd like you to begin by telling us who you are in more personal terms, where you were born, early influences on your life, education, and things like that.

JO: I can give you a brief overview from start to present.

TB: Please do.

JO: Looking backward in time, it might be considered I haven't traveled very far in my career. I was born in Texas, educated in Texas public schools, baccalaureate degree from Trinity University, in San Antonio, two years military at Lackland Air Force Base in San Antonio, and a Ph.D. degree in General Experimental Psychology from University of Texas (UT) in Austin. During the last two years as a UT graduate student, I worked as research psychologist with the behavioral medicine group of the UT/USAF Radiobiological Laboratory at Balcones Research Center, near Austin. From there, I took a combined five-year "sabbatical" away from Texas, which included a National Science Foundation postdoctoral fellowship in psychometrics and multivariate methodology at the L. L. Thurstone Psychometric Laboratory of the University of North Carolina in Chapel Hill, two years as Chief of Criterion Development for the Veterans Administration Central Neuropsychiatric Research Laboratory, and two years as Associate Professor of Psychology at Kansas State University, where I was also recipient of an NIMH Research Career Development Award. I returned to Texas, in 1963, as Director of the Research Computation Center of the University of Texas Medical Branch in Galveston and Associate Professor in what was then the combined Department of Neurology and Psychiatry. I was promoted to Professor with tenure,

⁴⁸ John E. Overall was born in Gonzales, Texas, in 1929. He received his Ph.D. in Psychology from the University of Texas in Austin, Texas. He received post-doctoral training at the University of North Carolina in Chapel Hill. After serving at the V.A. Central Neuropsychiatric Research Laboratory at the Perry Point V.A. Medical Center in Perry Point, Maryland, he joined the faculty of the Department of Psychology at Kansas State University in Manhattan, Kansas. He returned to Texas to join the faculty of the Departments of Neurology and Psychiatry at the U.T. Medical Branch in Galveston. He, eventually, transferred to the Department of Psychiatry and Behavioral Science of U.T. Houston Medical School for the remainder of his career. He was interviewed at New Orleans, Louisiana on May 9, 2001.

in 1967, and transferred at the same rank and title to the Department of Psychiatry and Behavioral Science of UT Houston Medical School, in 1978, where I remain to date.

TB: Where were you born in Texas?

JO: In Gonzales, Texas, approximately two weeks before Black Friday, in 1929. My father was a small-town lawyer, in Gonzales, and my earliest memories are associated with growing up in the Depression years. From the point of view of my family, the Depression extended and got worse for several years, as people exhausted their resources. In 1933 through about 1935, things were at their worst, so my family didn't have a whole lot of money when I was a child. My father occasionally took livestock and other produce for fees. Once he took a small herd of Spanish goats. He had them butchered and put the wrapped packages in a cold storage locker at the local ice house, which was what people did before home freezers came along. We ate a lot of goat chops, ribs, and sausage that year. Everyone had a hard time in those years and jobs were scarce. In spite of the shortage of cash, my mother was able to have a maid, who was a combination of housekeeper and cook, and who looked after me while my mother taught school to supplement family income. My maternal grandfather came to live with us, and he also devoted a lot of time to me. I started school in Gonzales at the same elementary school where my mother was teaching. Things continued to be bad during those years, and my father's law practice suffered a dramatic setback when the older lawyer, with whom my father worked, died. Soon after that, my father gave up and moved the family to San Antonio, where I entered the third grade.

TB: So you grew up in the Depression years and the death of your father's law partner had a significant effect on your life?

JO: My father had gone to Gonzales after graduating from law school to work with a successful older lawyer, the one who died. They shared the second floor of a building on the town square across from the courthouse. Things went well initially, but coincident with the Depression getting worse, the wife of the older lawyer died. As the story goes, the older man drank himself to death over the next year, while remaining night and day closed in his office. How much the Depression had to do with that is questionable, but it had a lot of consequences for my father and affected me in a big way, as well. Soon after the death of his mentor, my father reached a decision to accept a position as associate to a prominent lawyer in San Antonio, who had a suite of offices on an upper level of the Smith Young Tower, which was the only

“sky-scraper” in downtown San Antonio. The home in Gonzales was sold for whatever it would bring in the Depression. A moving van came, and the family was loaded into the car, together with personal belongings and a pet canary, for the trip to San Antonio. But at Luling, Texas, only about 35 miles from Gonzales, an oil company flatbed truck made a sudden left turn in front of our moving car, and an accident that totaled our car was unavoidable. While my father was arranging for transportation on to San Antonio, he called the office of the senior lawyer, with whom he planned to work in San Antonio, and learned that the lawyer, with whom he planned to work, had committed suicide by jumping out of his upper-floor office window. Now, my father had lost a second senior partner, whose guidance he had counted on to launch a long-term career. We arrived in San Antonio with little money, no car, no house, and no office, or associates to help in getting established. Those events helped place the move to San Antonio in context of the Depression, more than any other in my memory.

TB: Now tell me more about your life after the move to San Antonio.

JO: I don’t remember much about the remainder of my elementary school years. I recall getting into a fist fight when trying to stop a bully picking on my friends. I had never been in a real fight, and I thought I was getting the heck beat out of me. I went home a loser, even though it was mostly my pride that took the beating. I didn’t have a mark on me, and my parents insisted I get up and go to school the next morning. I felt a lot better when the bully showed up with a big blue shiner. I learned two lessons from that, which have remained with me to this day.

The Second World War came about the time I was entering junior high school. That ended the Great Depression but didn’t end its effects on my life. Early into the war, when most of the older boys were going into the service, I managed to pick up more home-delivery newspaper routes and delivered more newspapers than anyone else in San Antonio. That presented a problem for my attempt to fit into the teen-age social culture of a mostly upper middle-class high school environment. Students in the San Antonio school system were stratified into high, middle, and lower ability groups, but that tended to represent social stratification as well. I was put into a high ability class, but the correlation ended there. My father was still struggling to get his solo law practice going without any help and the family had no money to spare. I entered teen years feeling a need to begin taking care of myself. It wasn’t so bad. I made a lot of money for a teenager with my multiple paper routes. I had a car of my own, a liberal gasoline ration card because of my

newspaper delivery work, and on numerous days in the fall and winter, I got up in the wee hours to finish my morning paper routes in time to go duck hunting by dawn at a lake south of town. A friend named Richard Culpepper and I worked in the summers at an exclusive hunting club on the lake. We constructed deep-water blinds and nailed new palm-branch camouflage to others, replaced anchor lines, and painted the heavy wooden decoys for that day to look like bluebills, pintails or mallards. For that work, we two teenagers were granted full membership privileges, including breakfast at the club house and participation with the men in drawing bingo chips from a hat, which determined where each member was to hunt. Certain locations were better than others, depending on the wind and weather, but that didn't matter to my friend and me because we usually hunted the shoreline. I'm amazed at the energy I had in those days.

TB: Did you graduate from high school in San Antonio?

JO: I didn't, although I was beginning to integrate into the environment of a socially-stratified high school. In spite of my divergent interests, I joined a high school fraternity and was beginning to feel at home in San Antonio. But another big change occurred when my father retired, in 1946. His retirement, while I was still in high school, had a major impact, not only on my education, but for later life as well. I was 17 and a senior in one of the two large public high schools in San Antonio. My father had been working for much of the time to untangle the interests of 16 heirs to a country estate in which my mother owned a share. Working with the surviving heirs, one at a time, he cleared the title to the property by buying out or arranging financing with each of them. We then moved to that country place near a town named Round Rock in central Texas, about 20 miles north of Austin. My father always wanted to live in the country like he did when growing up. Round Rock is now a large suburb of Austin, where the Dell Computer factory is located, but in 1946, it was quite small. My graduating class at the Round Rock High School had something like thirty-five students in it, and that was a disappointment for a big-city boy from San Antonio. A mitigating factor was I made the football team and set track-and-field sports records in the smaller league. From there, I went to the University of Texas at Austin and stayed as long as I could with the Korean Conflict going on. When I was bussed to San Antonio for a draft physical, I decided it was time to volunteer for the Air Force.

TB: Tell us about your life at the University of Texas in Austin, before you joined the Air Force. You went there right out of high school?

JO: No, I skipped a step in telling about my undergraduate college days. I actually started college at Texas A&I in Kingsville, Texas. My parents were afraid I wasn't ready for the big time. It was the best educational choice I could have made. I did well in the curriculum there, got a good start by putting basic freshman college courses behind me, and was ready to transfer to the University of Texas, in Austin, after completing my freshman year. But I still wasn't ready to get serious about my education and where I was going after that. It took another important move to get serious. That came when going into the Air Force interrupted my tenure as a perennial undergraduate at the University in Austin. I had gone there for five years, in addition to the year at Texas A&I. After six years without receiving a degree, I was about to be drafted and volunteered for the Air Force. I was a late bloomer and didn't apply myself to study in my undergraduate days. That is why, when I try to recollect my undergraduate education, it is the other things I did that are most prominent in my memory. My slower pace at the University allowed me to support myself by working part-time during the school year and throughout each summer. I didn't attend summer sessions in college. Instead, I worked at a variety of jobs to help support myself and because I wanted to. I boast I held more part and full-time jobs for meaningful periods than anyone I have known in my subsequent life. I never wanted to be just a nerd or just a college professor either. I started working at age 14 and kept it up. That allowed me a range of experiences in the real world I treasure. I single-handedly hauled in tons of bailed hay the summer after we moved to the country and hefted it up to the rafters of a two-story barn at the family's new country place. That was viewed as keeping in shape. Subsequently, I measured cotton acreage for the Department of Agriculture one summer and worked at a cattle auction barn part-time during one school year. Apart from my agriculture-related pursuits, I worked as deck hand on a shrimp boat on the Texas gulf coast, a travel information agent on the Mexican border, in a canning factory, sold insurance, worked as a collection agent for a loan company, and worked on a railroad gang. Those were just a few of the thing I did while in school.

TB: You mentioned you were in the Air Force. Tell us about your military career.

JO: I didn't do the most heroic thing when my college draft deferment was running out. I decided to volunteer for the Air Force. At the same time, I was very much in love with my wife-to-be and didn't want to risk going off and leaving her. We got engaged before I took off for the Air Force. I made up my mind I would stay at one of the several air bases in San Antonio. I didn't realize

people don't just "make up their minds" in the military, but it happened to work out for me. I went through basic training at Lackland Air Force Base, in San Antonio, and stayed there the whole time I was in the Air Force. I went through a couple of Air Force schools, into an Academic Instructor's Squadron, and then on to Officer Candidate School. About the time I received my commission, President Eisenhower was elected, and decided to cut back the military. I was offered the opportunity to be discharged into the indefinite active reserve, and I took it. The Air Force made three important contributions to my educational progress. I had not received a baccalaureate degree before leaving the University for the Air Force, but Lackland Air Force Base was home to the largest concentration of psychologists ever assembled in what was called Personnel Laboratory, which had the primary mission of developing measurement instruments for pilot selection. Many people in that endeavor were young academic psychologists who wanted a teaching career but were there to fulfill their military obligation, as I was. Trinity University of San Antonio took advantage of this to open a program of night classes on the base, employing some of the young psychologists who wanted to teach. I took courses, and that, plus completing a couple of courses on campus in town, resulted in my finally receiving a BS degree from Trinity University, in San Antonio, rather than from the University in Austin. It is also how I ended up in psychology, rather than one of the other areas I had tried majoring in before I left the University of Texas. The third benefit provided by my Air Force experience was it gave me time to grow up. I got married and became serious about making something of my life.

TB: Was this in the early 1950s?

JO: That was in 1954. I left the Air Force, active duty at least, and went back to the University of Texas in Austin for graduate school, where I completed work on my Ph.D., in 1958. As a graduate student, I worked at the Radiobiological Laboratory of the University of Texas and the US Air Force on an Air Force contract. I didn't personally train the monkey, but that was where Sam, the "space monkey," trained to become the first primate in space. The broader mission of the Radiobiological Laboratory was to examine the effects of head and whole-body radiation on learning, memory, and performance. It was anticipated that atomic powered aircraft would soon become a reality, and there was concern about the effects of radiation on pilots. Rhesus monkeys were our primary subjects for the memory and decision-making studies, and rats were used for

studying the biological effects of radiation on activity level, endurance, and other kinds of physical performance radiation exposure might affect.

TB: Weren't you involved in conditioning research in those years?

JO: That is how I got to the Radiobiological Laboratory but wasn't what I ended up doing most of the time. They used various kinds of conditioning tasks for the monkeys in order to observe their performance on learning, memory retention, and discrimination tasks and see how head or full-body radiation affected those abilities in the short and longer term. A famous test instrument used for these studies was the Wisconsin General Test Apparatus. A monkey was placed in a small cage with a closed door separating it from a tray with stimulus objects on it. When the door was raised, the monkey received a token food reward for choosing the correct stimulus object. Ironically, the monkeys performed better after radiation. I think it must have been because they were less distractible and didn't nervously turn round-and-round in the cage, like impatient monkeys are prone to do. The radiated monkeys just sat there and paid attention to the task. Although improvement in performance was certainly not what was expected and might have been a hard sell as an effect of radiation, psychologists made the most of it, and produced a series of papers elucidating a new "theory of distractibility." My work there is when I first concentrated on statistics. My primary role at the Radiobiological Laboratory became analysis of the data using a Frieden desk calculator. The calculator the Air Force contract bought was top-of-the-line, called a "square root Frieden" because it had a built in capability to take the square root of any number, large or small. That was in addition to adding, subtracting, multiplying, and dividing. I turned out several reports to the Biomedical Research Support Center of the Air Force, which was then located at Randolph Field, and I participated in or supported a number of publications in psychology and related journals reporting, and trying to explain, the "negative results" from studies in which radiation appeared to enhance performance. The work was also important for my being awarded a National Science Foundation postdoctoral fellowship after receiving my Ph.D.

TB: How did you get involved in statistics?

JO: My interest in statistical methodology was stimulated by my work as a graduate student at the Radiobiological Laboratory and by taking advanced courses in experimental design under a distinguished professor, Lyle V. Jones, who spent a year at the University in Austin, while on sabbatical from the University of Chicago. He was an impressive scholar and seemed to take an

interest in me. He went back to the University of Chicago, briefly before he moved to head up the Psychometric Laboratory at the University of North Carolina in Chapel Hill after the death of its founder L. L. Thurstone, the psychological measurement and multivariate statistics icon. Thurstone had himself moved there upon his retirement from the University of Chicago. As a consequence, I decided to take my NSF postdoctoral year in the Psychometric Laboratory at UNC, after being invited and sponsored there by Lyle Jones. The Psychometric Laboratory provided a good environment for self-directed study and, separately, the Department of Statistics at the University of North Carolina at Chapel Hill also had a concentration of statistical expertise in multivariate methodology. The Statistics Department at UNC was a participant in the Research Triangle Statistical Institute, which combined the talent from three different institutions. The Department of Statistics at UNC in Chapel Hill provided the primary theoretical and multivariate component, North Carolina State University at Raleigh was known for contributions in experimental design and applied statistics, and Duke University in Durham provided an educational focus. Most of the courses taught in the Department of Statistics at Chapel Hill were beyond my training as a graduate student. I, nevertheless, enjoyed the atmosphere the setting provided, and some of the outstanding scholars in the area of multivariate analysis occasionally came over to the Psychometric Laboratory to give scaled-down lectures for the trainees. I only realized later how much I absorbed.

TB: So, this is how you became involved in statistics?

JO: I did not know what I was going to do after my postdoctoral year. It was 1959 by then. I contemplated taking a temporary position in the Department of Psychology, at UNC, but the only thing offered was a temporary teaching slot in Social Psychology. Then a real break came in the form of an invitation to join the staff of the Veterans Administration Central Neuropsychiatric Research Laboratory at Perry Point, Maryland. As an inducement, I was offered the title of Chief of Criterion Development. The move offered three advantages that provided an entirely new and lasting direction to my career. First, the Central Neuropsychiatric Laboratory had the responsibility for design, monitoring, and analyzing data from the large-scale controlled studies of chemotherapy in psychiatry pioneered by the VA soon after the arrival of chlorpromazine from France, in the early 1950s. Unparalleled volumes of data, descriptive of psychopathology from a broadly defined psychiatric patient population, were arriving at the Central Neuropsychiatric Research Laboratory

on which I could apply my newly acquired multivariate statistical analysis methodology. As Chief of Criterion Development, I had access to a voluminous database from which to distill the dimensions of manifest psychopathology that would lead to rating-scale quantification, the best known of which became the Brief Psychiatric Rating Scale (BPRS), which I authored in collaboration with Donald R. Gorham, in 1962. The second major advantage was that it served as an arm of the VA Central Office in Washington. It was not administratively tied to the Perry Point VA Hospital, although it was located on the extended hospital grounds. The Central Neuropsychiatric Research Laboratory had a separate Advisory Committee, composed of senior VA clinical investigators from around the country, who met at the VA Central Office in Washington, DC three or four times a year. My immediate boss, Julian J. Lasky, myself, and two other psychologists from the Perry Point Laboratory were expected to attend the Advisory Committee meetings. The Central Office support for the research coordinated by the Perry Point Laboratory also included sponsorship of an annual meeting for the larger number of VA doctors and others who voluntarily collected data for the early large-scale VA “Cooperative Studies of Chemotherapy in Psychiatry.” That was important for me becoming acquainted with key people in clinical psychopharmacology research, the most important for my later career being Dr. Leo Hollister, with whom I formed a long-term collaborative relationship that continued for more than two decades after I left VA employment. At the time I first met him, Leo was chairman of the Advisory Committee with which we met at the VA Central Office in Washington. Third, and most important for my contribution to assessment in clinical psychopharmacology research, was the almost simultaneous arrival at the Central Neuropsychiatric Lab of Donald R. Gorham, who partnered with me in the development and initial testing of the Brief Psychiatric Rating Scale. Don Gorham was an older seasoned clinical psychologist, who was invaluable in providing clinical insight and rating-scale experience. He arrived with a reputation for development of the Gorham Proverbs Test, based on the importance of loss of abstract thinking ability among the earliest clinical signs of major mental illness. Another important lasting relationship that originated in the VA Central Neuropsychiatric Research Laboratory was with C. James Klett, who arrived as Associate Director of the Perry Point lab, two or three years before Don Gorham and I. Ten years later, Jim Klett, and his wife Shirley, spent a summer in Galveston working with me to finish up a book entitled *Applied Multivariate Analysis*, which Jim and I coauthored, in 1972.

TB: It seems the laboratory had an impressive staff?

JO: I guess it did. The lab was already in possession of a tremendous body of collaborative studies data when I arrived. What was called Project Three was finishing up at the time I arrived. Project One, as I understand it, was the stimulus for placement of the laboratory at Perry Point. It was to be a Central Office auxiliary, located on the grounds of the VA Center at Perry Point, Maryland, but not administratively associated with the hospital there. It was first formed to organize, monitor, and analyze data from the Lobotomy Project, which later became known as Project One of the series of cooperative studies that followed. Lobotomies were common, especially before effective drug treatments became available, but even then, the procedure was questioned by many. The VA decided it was time to do something one probably couldn't ethically do today, conduct a controlled study of the utility of the lobotomy procedure for treating psychiatric illness. About halfway through the Lobotomy Project, the VA stopped doing lobotomies, and that ended the research project. As far as I know, the results were never even looked at because the scientific community had decided it was not politically correct, even though about half of the originally planned patient samples had been entered into the study. Chlorpromazine had just come from France in the early 1950's; with it came excitement and controversy about the value of drugs for treatment of patients with major psychiatric disorders. It was decided within the VA hierarchy that nothing should delay undertaking a well-designed controlled study to settle the question of efficacy, once and for all. Project Two of the VA Central Neuropsychiatric Research Laboratory was the pioneering multi-center double-blind study of chlorpromazine versus placebo. It became the prototype for clinical trials in psychopharmacology, with double blind, randomized, placebo controlled, repeated measurements. All things that remain state-of-the-art for controlled clinical trials to this day. And it started there at the VA Central Neuropsychiatric Research Laboratory, where my association with clinical psychopharmacology research also started. When I arrived at Perry Point in 1959, they were just finishing up Project Three, which involved comparative evaluation of the efficacies of five or six new phenothiazine drugs that came along soon after chlorpromazine appeared to be an effective treatment. More important for me was the body of multivariate data these studies produced. It included descriptive rating-scale data from a lengthy instrument authored by Maurice Lorr and others from the VA Outpatient Research Program. It was called the Multi-dimensional Scale for Rating Psychiatric Patients (MSRPP), and I believe it consisted of 63 ordered-category

rating-scales, including a few binary items. The VA collaborative studies provided those data on hundreds of patients, which I used as a resource for identifying the parsimonious set of basic dimensions of manifest psychopathology underlying the larger body of descriptive data, which in turn served as a basis for development of the Brief BPRS.

TB: So the BPRS was a contribution that actually originated as part of your responsibilities at the VA Central Neuropsychiatric Research Laboratory? It has made a lasting impact on clinical psychopharmacology research. Please tell us more for the record how it came about and some of the work you did with it.

JO: The first thing that needs to be emphasized is the important contribution to development of the BPRS that was made by Don Gorham. I was a budding methodologist when I came to Perry Point with no clinical experience. It was Don Gorham who brought the clinical insight and experience. He was twenty years my senior. I contributed the statistical methodology for identifying the primary factor structure underlying correlations among the larger, somewhat redundant set of rating-scale and binary-response items of Maurice Lorr's Multidimensional Scale for Rating Psychiatric Patients. Don's contribution was clinical interpretation, recommending clinical names for the primary dimensions of manifest psychopathology, and choosing the particular rating-scale nomenclature that constitutes the BPRS today. Actually, there were more steps in development of the present instrument than I have said here, but this should be adequate to provide understanding of the close working relationship that Don Gorham and I had during my time at the Perry Point laboratory. Don left the Lab to become Chief Psychologist at the Bath VA hospital near his retirement home at the top of a hill overlooking Lake Cayuga in upper New York State. The only other thing I would say about what I did with the BPRS is that its popularity in clinical psychiatric and psychopharmacology research today is partly due to my continued use of the multivariate measurement data that it provides to illustrate and evaluate new methods for the analysis and interpretation of clinical data across a decade or more since the BPRS was first published. My uses of the BPRS data included illustrating a new method of direct factor analysis, applications of cluster analysis methods to identify naturally occurring homogeneous sub-groups of patients with distinct profile patterns and use of BPRS profile patterns in the search for subtypes that are most responsive to different variants of the newer psychotropic drugs. Time has erased the relevance of much of that work, with orthogonal and oblique rotations of principal axes

factor solutions replacing direct factor solutions. The search for specific indications of new drugs within the broader categories of psychiatric illnesses, are largely failing to produce clinically useful results. The work helped, however, to keep the BPRS before the public eye, where new interests in its applicability continued to emerge. My own work having the greatest contribution to wider use of the BPRS would likely be considered introducing it to a larger international psychiatric research audience through collaborative publications with leaders in European psychiatry, which originated, for the most part, from my membership in the CINP. The most important impetus for the BPRS came, however, when Jonathon Cole, as head of the NIMH Psychopharmacology Service Center and subsequent Psychopharmacology Research Branch, foresaw the utility of establishing a central analysis and depository for data collected in NIMH-supported clinical drug trials. Particularly those conducted by the group of ECDEU and later NCDEU investigators, where the BPRS was selected to provide a single common thread of descriptive data running across the studies involving antipsychotic drugs and the Hamilton Depression Rating Scale (HAM-D) for studies in the treatment of depressive disorders. The original Clinical Psychopharmacology Service Center became the Psychopharmacology Research Branch of the NIMH; and the satellite Biometrics Laboratory under the direction of Roland Bonato was established at George Washington University to accomplish the statistical analysis and data management functions originally envisioned by Jonathon Cole and his associates. The leadership of the program at the NIMH Psychopharmacology Research Branch, under one or another of its organizational name changes, was assumed by Jerome Levine, when Jon Cole retired and moved to head Harvard's McLean Hospital in Boston. Through all of these evolutionary changes, the BPRS became familiar to an increasingly large proportion of clinical researchers in the United States and for many abroad.

TB: It seems you developed numerous important relationships in those years. Would it be fair to say your relationship with Leo Hollister played an especially important role in directing your career toward clinical psychopharmacology research?

JO: Yes, and membership in the ACNP, as well. Of the early relationships formed at the Central Neuropsychiatric Research Lab in Perry Point, Leo Hollister was the most influential in directing my later career toward clinical psychopharmacology research. He was a charter member of ACNP, helped organize the first formal meeting, and later became President of the organization. I was not a charter member, but under his shadow, I attended the early meetings and was voted into

membership by the 3rd or 4th annual meeting. Leo Hollister was also instrumental in my election to Member and then Fellow of the CINP, which in turn introduced me to leaders in international psychiatry and psychopharmacology research. This led to several collaborations and enduring relationships with leaders in European psychiatry, including most prominently with Professors Pierre Pichot in Paris, Hans Hippus in Munich, and Max Hamilton in Leeds. Charles Pull from Luxembourg spent a year as a young man studying with me, while I was professor at the University of Texas Medical Branch in Galveston, as did Filippo Gabrielli from Genoa, Francisco Gomez-Monte from Mexico City, and Peter Reichertz from Bonn, who went back to Germany to become a leader in founding of the German Society of Medical Infomatics.

TB: We are still at Perry Point, Maryland. Where is Perry Point?

JO: It was geographically isolated, about 35 miles north of Baltimore and the same distance west of Wilmington, Delaware. Day-to-day interaction was confined to the Point. Some have characterized the social environment as the “Peyton Place on the Susquehanna.” But that is all I know about that. I would like, however, to describe the physical environment I found at Perry Point. It was the most interesting outdoor environment I have encountered throughout my career, rivaling Galveston, where I lived following my return to Texas. The Central Neuropsychiatric Research Laboratory was located on the Perry Point VA Hospital grounds, in an old cement block building left over from DuPont Company, manufacturing munitions in WW-II. The setting offered numerous enticements. Housing on the hospital grounds, also left from the WWII war, was conveniently near work and very economical. Our two-story house cost less than \$40 per month to rent with heating oil and electricity included. The hospital grounds were on a delta formed by the Susquehanna River where it entered Chesapeake Bay. A boat dock with slips for centerboard sail boats was located about one block from our front door. Sailing was great across delta flats with tall waving sea-grass almost to the surface of the clear filtered water. There were places to sail to, unlike sailing in the Gulf of Mexico after later living on Galveston Island. You could sail around the Turkey Point entrance to the Delaware Cut or picnic on an island belonging to the Army’s Aberdeen Proving Ground. Fishing for striped bass and shad was good in the mouth of the Susquehanna River. Herring ran up a small stream on the Point each spring to spawn, and Don Gorham challenged me to wade in the water with chunks of ice floating by to catch the herring in a seine. We netted buckets. After attempting to make pickled herring ourselves, we tried to give

the rest to neighbors, but nobody seemed to want them. The one down side was that winters on Chesapeake Bay were cold and damp with lots of snow.

TB: All in all, you seem to have found your position at the VA Central Neuropsychiatric Research Lab good professionally and you liked the Perry Point environment. Still, eventually you left Perry Point. Why did you decide to move, and where did you go?

JO: You are right about my professional experience with the VA in Maryland. I had ample resources readily available for my work, had expanding professional interaction both within and beyond the VA, and did enjoy the outdoor environment. I, nevertheless, had, in the back of my mind, an original graduate-student interest in becoming a university professor. At the same time, I was ambivalent about giving up the relationships and work that I had started at the VA Central Neuropsychiatric Laboratory. Two developments seemed to solve my problem. Leo Hollister, with whom I had already begun to form a collaborative relationship that lasted decades, embarked on a pathway separate from that of the ECDEU, in which he had a leadership role from the beginning. I do not know the full story, but he formed a smaller splinter group of collaborating VA psychiatrists that was more flexible in pursuing the early testing of new drugs and introducing new ideas into the process. He invited me to be involved in the new endeavor from a design and statistical analysis point of view, and I arranged to continue in that role if I moved to Kansas. The other enticement that helped tip the balance was the offer of an unusual opportunity to move directly into a senior faculty position at Kansas State University, even though I had no previous experience as a college teacher. How that occurred is a long story, but it was facilitated by the fact that Professor Harry Helson, from my graduate student days at the University of Texas, moved to K-State when he retired from UT in Austin. It was he who nominated me to fill a vacant faculty position there. I went to Manhattan, Kansas for a series of interviews after which I was offered a job as Associate Professor of Psychology at Kansas State University, with the side condition that the department chairman at K-State would sponsor and support me in application for a NIMH Research Career Development Award, which I was granted soon after my arrival. Another side agreement was that I could use the award to continue working with Leo Hollister, which I did, while carrying a teaching load of only one course in the fall and one in the spring semester each year. Leo was generous with the credits, and I continued to build a resume of first and second authorships related to clinical psychopharmacology research. In spite of the light teaching load, I

discovered I did not like to spend time preparing lectures for relatively few students. Publishing in clinical and methodological journals reaches a lot more people and is, unfortunately, more rewarding for academic advancement and tenure.

Life in Kansas was otherwise most enjoyable. The other faculty members and people in the community were quite a change from interactions with the outside community in the Baltimore area. In fact the warm, open, and generous Kansans were like the people in Texas. I learned, upon my return, that Texas was rapidly changing during this period, as larger cities and economic interests began to dominate. As an example of the Kansas culture at the time, one of my new faculty colleagues at K-State, Donald Trumbo, and I became acquainted with a family that operated a farm and ranching operation of a couple of thousand acres in western Kansas. Pheasants were especially plentiful out that way, and Don Trumbo and I were invited to come and hunt on their place each year. We went after Thanksgiving dinner and again during the Christmas break; and our Kansas host didn't just let us hunt on his property but took the day off to drive us around in his pickup truck, letting us off on one side of a section of sage brush land and driving around to the other side to pick us up later. There was a lot of sage brush because, at the time, the government was paying to leave it idle for the good of the land and to hold up prices for wheat by limiting production. Sage brush is waist high and is hard to walk through, but a pheasant springing up every 15 feet or so made it quite enjoyable. Pheasants were so plentiful that each trip we got our two-day legal possession limit in morning and afternoon hunts the first day out. I later came to suspect that the land owner operated a hunting guide business on his land during the winter, when there was little other work to do, but he treated us like old friends. I also bought an 80-acre farm near Manhattan, Kansas where K-State is located. It had an old two-story house and a storm cellar for tornadoes. I bought a John Deere tractor and planted a garden too large to harvest, but I rented out most of the land to a farmer who planted wheat and soy beans. Regarding the oversize garden, what else do you do with a real farm tractor but to cultivate an oversize garden? I harvested all the produce we could use, gave away to friends and neighbors all they would take, and left the rest for rabbits and coons. I have always needed to counterbalance academic life with something less cerebral.

TB: It seems that you fit into the Kansas State University environment very well, but again you eventually decided to move. What prompted you to move from Kansas?

JO: Out of the blue, I received an invitation to be considered for a job with the University of Texas Medical Branch in Galveston. Truth is that I missed Texas, where I had grown up, gone to school, and where my parents, my wife's parents, and numerous other friends and family remained. I also must admit that I was offered twice the salary I was making at K-State. I accepted the job to become Director of the Research Computation Center of the institution and Associate Professor in the combined Department of Neurology and Psychiatry. There were soon to come, other medical schools in Texas, but the Galveston facility proudly kept its designation as the Medical Branch from a time when the medical school was viewed more like a division or college of a main university rather than a separate institution. It was also the only medical school that continued to receive state funding for hospital operation and patient care. In return, it had an obligation to accept a large quotient of patients from other parts of the state. That was partly a matter of its historical precedent, but also because the school had outgrown its patient base on Galveston Island. The reason why the Medical Branch was located in Galveston in the first place, rather than in Austin with the main university, was because Galveston was the only city in the state with a population large enough to support Texas' only medical school, when it was founded in 1889. Life on Galveston Island offered numerous possibilities. After little more than a year, our new house on a bulk-headed inlet from the protected back side of the island, was completed. The first year we lived there, I caught speckled trout off that bulkhead before I got dressed for work. Our house was about eight miles from the medical center, and many days I would ride my bicycle down the sea wall to work. I had a Sailfish boat on our pier behind the house, and I soon acquired half interest in a 27-foot Norwegian folk boat with a 2000 lb. keel for sailing in the Gulf of Mexico. Later, we built a weekend cottage on the Neches River in the heart of what was to become the Big Thicket National Preserve, and from there I turned to fishing for large-mouth black bass in a couple of the numerous large reservoirs that span east Texas. Life at work turned out to be less tranquil than at the lake or shore. There was a competition between business and academic interests for control of computer resources of the school. The business side had a much bigger computer. IBM involvement in the business operation was great enough to justify six IBM employees on-site full time. The business computer facility was in the Medical Branch organizational chart, under the Vice President for Financial Affairs, while the smaller Research Computation Center was under the Academic Dean. Just days after my arrival, the Board of Regents swooped down on Galveston

Island to fire the Dean, to whom I was to have been responsible, while the Vice President for Financial Affairs went on to Austin to become Chancellor of the whole University of Texas System. Even within the Research Computation Center, a palace revolt was brewing for control. The woman who had previously headed the operation was a close friend of the next appointed Dean, who was also institutional PI on the NIH grant that funded the Center when I arrived. After three years, I decided that administration was not my calling. When I received the first installment of the grant that was to support my work for the next 32 years, I slipped quietly over to my academic appointment as Associate Professor in the Department of Neurology and Psychiatry. At about that time, Neurology and Psychiatry split into two separate departments, and my appointment was thenceforth in the new Department of Psychiatry and Behavioral Science. I was promoted to Professor after four years in Galveston. In the meantime, I was a member of a NIMH Review Committee for which the committee chairman was a Boston University psychiatrist, who had a large NIMH grant to study the stress effects on air traffic controllers of observing “near misses.” I was impressed with his leadership qualities as chairman of the NIMH review committee, on which I also served. When the aging chairman of the UTMB department of psychiatry prepared to resign, I pushed hard, in and around official channels, for the man I had come to know through the NIMH committee to replace him. That was a very big mistake for me and the department as a whole. When my favored candidate was appointed to be the new chairman of the Department at Galveston, he came with the idea he owned everyone in the department. He refused to endorse my grant renewal application, saying he did not want me to do what I was proposing but to be the “department statistician” instead. By coincidence, the retired but politically powerful former President of the Medical Branch was called back into service by the Board of Regents to serve as temporary President in activating the new University of Texas Medical School in Houston. He facilitated my transfer to the new medical school at the same rank, tenure, and title I had in Galveston. I had the site visit on my grant renewal application in Houston before I moved there myself.

TB: You made passing reference to both the ACNP and ECDEU. Could you say something about your involvement?

JO: My recollections are more from participation in the Early Clinical Drug Evaluation Units. I was not a charter member of either organization, but I believe I became affiliated with the ECDEU

as a collaborator of Leo Hollister, no later than its second or third meeting. At that time, the aim of the ECDEU organization was to provide very early evaluation of new drugs independent of drug company control. The new NIMH Psychopharmacology Service Center, under the leadership of Jonathan O. Cole, was responsible for the origination of the NCDEU program. The initial membership consisted of 10 or 12 senior clinical investigators who were seated around one long conference table on the NIH campus in Bethesda, Maryland. Younger associate members, like I was for the first few years, were seated in chairs around the wall.

Actually, “membership” was not as clearly defined as it was for the ACNP, which was organized more like a college fraternity. The senior members of the ECDEU were not only recognized clinical researchers in their own right, but participation was encouraged by the fact support, in the form of a grant from the Psychopharmacology Service Center, was virtually assured. The discussion at these early ECDEU meetings was largely a kind of “show-and-tell” about what new drugs appeared interesting and what the senior investigators had been doing with them over the past year. In spite of this, a metamorphosis occurred as the research interests of the ECDEU clinical investigators moved from open-label, very early testing of new drugs toward more controlled, double-blind studies aimed at demonstrating the efficacy of new drugs in a more controlled experimental design. The name of the NIMH program and research units supported by it was accordingly changed from “Early Clinical Drug Evaluation Units” to “New Clinical Drug Evaluation Units” (NCDEU). It is important to mention that investigators, like those in the ECDEU and ACNP programs, were, for the most part, still acting as individual clinical researchers responsible for all aspects of their studies from conception and design to data collection, management, and analysis. Memberships in both organizations expanded, and cohesiveness began to disappear.

TB: Can you remember who the original ECDEU investigators were when the meetings were held around that single table on the NIMH campus in Bethesda?

JO: I am not sure I can do that with confidence. There was a lot going on in clinical psychopharmacology in the early 1960’s. I was privileged to be involved at various levels in three overlapping programs, the ECDEU, ACNP, and VA. I interacted with investigators I viewed as key players in all three venues. It has been a pretty long time now, and it is quite possible I will confuse memberships in the ACNP and ECDEU, in particular. I may need your help to fill in

where I blank out on this. I remember you were there and I remember the occasions and the contexts better than I am able to separate which particular individuals may have been in one, but not the other of the primary groups. In many cases, they were the same individuals.

TB: Am I correct you said that you got involved with ECDEU via Leo Hollister?

JO: Yes, Leo was one of the original ECDEU members. I had established a collaborative relationship with him while I was at the VA Central Neuropsychiatric Research Laboratory at Perry Point, and he was chairman of the Oversight Committee for the Laboratory. About the time I was preparing to leave the VA for K-State University, Leo was getting impatient with the cumbersome VA research program and contemplated forming a smaller splinter group of actively collaborating VA investigators. He asked me to join him for the contribution he expected me to make to design, statistical analysis, and methods section of research reports. He received a grant through the ECDEU program to support his proposal for this smaller, more actively collaborating group of VA clinical investigators, and I came aboard to participate. He remained an active member of the ECDEU all the while, and I just accompanied him to those earlier meetings without thinking much about being invited. I was also busy trying to adapt to the new role as college professor, preparing lectures, and beginning to question whether I wanted to be a college professor for the rest of my life.

TB: Can you recall some of the early recipients of the NIMH grants that were a foundation for the ECDEU program?

JO: In addition to Leo Hollister, I think of Heinz Lehmann as probably one of the original ECDEU investigators. Barbara Fish, the lone child psychiatrist in the original group, was the mentor for the younger Magda Campbell, in much the same way Leo Hollister was for me. I wouldn't be surprised if Magda had about the same early involvement with ECDEU that I did. Sidney Merlis comes to mind as a probable charter member. An English physician named David Wheatley did outpatient anxiety and depression studies. I remember his faithfully attending the ECDEU and the later NCDEU annual meetings, but I am less confident that he was there from the beginning. Similarly, Karl Rickels at Philadelphia, concentrated on taxonomy of outpatient anxiety and depression in relation to pharmacologic intervention, but he may have entered the ECDEU program about the time I did. I recall his mentioning his NIMH psychopharmacology research grant had the same origination date as mine. Eugene Paykel, an English psychiatrist later at Duke

University, had similar interests in defining taxonomy of anxiety and depression and relating it to differences in drug treatment response, but I think he probably joined the NCDEU program a bit later. Richard Whittenborn was a psychologist identified with the earliest days of the ECDEU program. He later held the office of Secretary-Treasurer of the ACNP for many years. I believe that Dick also authored a rating scale used in one of the earliest VA controlled treatment evaluation studies, before Don Gorham and I joined Perry Point VAC and which preceded the BPRS. Another psychologist that figured prominently in ACNP history was Albert DiMascio, in whose name an annual memorial lecture is presented at Tufts University. A number of other psychologists with strong methodological orientation supported the ECDEU through administrative roles in the Psychopharmacology Service Center and its successor, the Psychopharmacology Research Branch. A name that comes to mind from that group is Dean Clyde, but there were others as well. I mentioned Ron Bonato in connection with his work as head of the NIMH/George Washington University satellite computer center, founded to accumulate assessment data for patients in the NCDEU clinical trials. I don't know when Jerome Levine joined the intramural group because in a bureaucratic environment it takes even talented young people time to reach a level of visibility, but there is no doubt about the contribution he ended up making as successor to Jonathon Cole. Alice Leeds entered the picture at about that time, was a friend and critic of everyone, and will be remembered for her editorial role in helping the NIMH supported Psychopharmacology Bulletin reach the audience for which it was intended. I liked to publish my work in that journal because I was communicating to the clinical investigators with whom I had an identity. I have strayed from the question of who were the founding participants in the ECDEU program. Can you remind me of other I have failed to recall?

TB: George Simpson and Don Gallant were there from the beginning.

JO: They were definitely there early on. I believe there were no more than about eight or ten original recipients of the Early Clinical Drug Evaluation Unit grants. I have undoubtedly named a number that were not in that group at the beginning, but I remember them all as contributing in recognizable ways to shaping the course of early clinical psychopharmacology research through participation in the ECDEU, ACNP, or in both. There was, however, another psychiatrist I believe Jonathan Cole may have brought aboard the Psychopharmacology Service Center staff to interact specifically with the ECDEU investigators. He was not slow in gaining visibility; but, as I recall,

he wasn't very popular in that role. I can't recall his name and I am not sure he was a member of the NIMH in-house staff.

TB: Could you be thinking about George Crane?

JO: I am sure that is his name. He was an astute clinician onto something important about serious neurological side effects of the early phenothiazines that ECDEU investigators were not eager to hear about. I don't know whether George Crane is responsible for the naming, but he was certainly important in linking the frequent occurrence of tardive dyskinesia to psychiatric drug treatment. When he presented his observations at an ECDEU meeting, he was almost ridiculed out loud in the meeting, and certainly in an after-hours meeting of several members at a cocktail lounge of the Bethesda Naval Hospital across the street from where the NIMH was located. I was quite young, and naturally my opinion mirrored that of the senior members I was pleased to accompany. George Crane's popularity was not increased when he presented the plan for ECDEU participants to collect specific data that could be combined across centers for further analysis at the George Washington University Biometrics Laboratory. The BPRS was to be used in studies involving the testing of antipsychotic drugs and the Hamilton Depression Scale was to be the common data collected across studies involving depressed patients. I guess that none of the independent-minded senior investigators liked to be told what they were to do, and maybe it was contributed to by how George Crane came across. He just didn't have a politically-correct way of doing things. That is too bad because his contributions to the ECDEU program and to clinical psychiatry were really important.

TB: We have talked about your early involvement in ECDEU and NCDEU. You did mention the importance of relationships that you developed with European psychopharmacologists and psychiatrists through your affiliation with the CINP. Would you enlarge on that?

JO: The CINP has not been just another organization for me. It has produced collaborations that introduced much of the world to the Brief Psychiatric Rating Scale through a series of papers, in which it was used to compare and evaluate the consistencies and differences in psychiatric diagnostic concepts in different countries. Of even greater importance to me, personally, has been the associations formed with prominent psychiatrists, psychologists, and psychopharmacologists in different countries. While my difficulty in distinguishing between the important early associations in ECDEU and ACNP has been apparent, that is much less true of the early influences on my personal and professional career that can be attributed to affiliation with the CINP. I

mentioned some of their names earlier, but it might perhaps be interesting to mention a few personal memories of those important influences on my life and thinking. Somehow, I see them more clearly as individuals than many who were closer to home. A rather humorous incident occurred at a WHO sponsored meeting in Belgrade early in my affiliation with CINP. It was at a meeting of several days duration, and Max Hamilton was the appointed chairman. His autocratic handling of discussion and the discussants began to create a feeling of resentment as the meeting went on. As the acknowledged pioneer in clinical rating scale development and due to the popularity of his HAM-D rating scale for depression, he may have felt competitive regarding the BPRS. From the chair, he verbalized his opinion that the different rating constructs in the BPRS were not adequately defined. He punctuated his criticism by singling out the BPRS rating construct Hostility and saying in a raised voice, "Hostility, I don't even know what that means." The crowd in attendance broke into a tension-relieving round of laughter. I would not even mention this except for the lasting friendship Max Hamilton and I developed after that. He visited me in Galveston twice and stayed as a guest in our home. He was really warm and personable when you got to know him. Another lasting memory from that WHO meeting in Belgrade, which was attended by many CINP members, was a planned dinner in an old fortress on a high bank overlooking the Danube at the village of Novi Sad. I was seated beside Dr. Oldrich Vinar on the bus that took us there, and I remember well it was the day we all heard of the Russian takeover in Prague. No one knew that it was to be the last occasion any of us would see Dr. Vinar for a long time. He went back to Prague and was not permitted to leave the country for years. A psychologist named Engelsman had accompanied Vinar to the Belgrade meeting, but he didn't return to Prague and went to Canada instead. I think he may still be there.

TB: Yes, he has remained in Canada and is working there.

JO: Reflecting on what I have been saying about my European acquaintances, it is interesting how differently I have spontaneously designated them a formal title or not. Most are professors in their home institutions. I have used no rank or title in mentioning our ECDEU and ACNP colleagues. Most are friends whom I have known for years. It is customary for me not to identify friends by title. I might use titles in introducing them, but not when I identify them in conversation. On the other hand, there are certain European colleagues who are always Professors in my mind, even though I have known them long and consider them friends as well. In particular, there are *Professor*

Pichot and *Professor* Hippus. Nevertheless, I have always been awkward in making introductions. I have never forgotten when I introduced Professors Pichot and Hippus to my wife the first time she accompanied me to a meeting where both were present.

I believe it was probably CINP. In attempting an introduction I said, “Peggy, this is Professor Pichot and this is Dr. Hippus.” Try to work your way out of that one! We were, in later years, invited to the homes of each of them, so I suppose I have been excused. But I haven’t forgotten that faux pas to this day. There are people in Europe that remain always Professors. I actually met Professor Hippus somewhat earlier when he was at the Free University in Berlin. He had invited me to consult and perhaps to give a talk, I don’t remember. Soon after that, he was appointed to Kraepelin’s former chair in Munich, where he invited me to give a talk and entertained my wife and me for dinner in his home. I remember that visit because it was the beginning of Christmas season, when the local vendors were constructing their stalls for the Christmas Market in the center square in Munich. It began to snow, making a picture of the Christmas Market in my mind like I have seen on postal cards from friends, visiting there in later years. European collaborators and acquaintances, one way or the other tied to CINP, have been so generous and personally cordial to me that I have debts I can never repay. Some were senior academicians like Giovanni Cassano in Pisa, who I identify in my mind as among early proponents of computer technology in European psychopharmacology and whose conversion of an authentic farm house, with quarters for cows included, was an elegant setting for entertaining groups of visitors, in which I was included on occasion. From an historical perspective, I remember Jules Angst, in Zurich, giving me a personal tour of the hospital he inherited when named to the Chair Bleuler previously occupied. Others, like Professors Gioberti and Rossi in Genoa, Pichot in Paris, and Jose Carranza in Mexico City helped to arrange for their junior associates to study with me in the U.S., mostly at the UT Medical Branch in Galveston. Among them all, Professor Pierre Pichot stands out for his long and generous support of my career and what I value as a personal relationship. I am sure that is not unique for him, but I value it nonetheless. He has personal relationships with psychiatrists and psychopharmacologists throughout much of the world without letting international politics stand in the way. There are many memories that remain from long acquaintance with Professor Pichot. A scholarly French professor, with pipe and hat, he was active in his local medical society and international psychiatric circles as well, but on Friday afternoons

he closed his office to catch a train for the weekend in a small village south of Paris where he had a cottage and a different set of acquaintances. My first memory of him is associated with attempts to meet for an appointment at his office in the hospital of Saint Anne. I knew it was in the region of the Sorbonne, but I had failed to get adequate instructions on how to find him. I wandered into a likely looking building with a long dimly lit corridor ending with light coming from a room on the left. When I entered, I saw two scholarly gentlemen bending over manuscripts or maps on a table in an otherwise bare room. After I waited quietly before clearing my throat to interrupt them, they inquired of my mission. I asked if they could direct me to the office of Professor Pichot. They could not seem to understand who it was I said I was looking for. After several attempts to repeat, one of them produced a tablet and pencil and asked me to write down the name. They looked at what I had written and exclaimed in unison "Ah, Pichot!" It sounded like what I had been saying, but obviously not to the French ear. Another memorable visit to Professor Pichot's office occurred on the very day of the beginning of the student riots in Paris around 1968. I had taken a room the night before at a two-star hotel on Rue Ecole, about two blocks west of the Sorbonne. When I stepped out the door in the morning, I saw a double cordon of police in riot gear, holding small grey shields, blocking the avenue in front of the university. I don't remember how I got in touch with him, but Professor Pichot said to wait at the hotel and he would send a resident to take me by car around the disturbance to his office. The morning was quiet enough at his office in the Hospital, and he suggested we go to a nearby café for lunch if it isn't too crowded. When we walked in, there were only two other occupants at one of the tables in an otherwise empty café. When we left to go to his apartment, which was up the hill from the Sorbonne and across street from the French pantheon, a policeman stopped us at the corner. We could see the crowds below us down avenue St. Michelle and smell tear gas in the air. After some discussion in French, the officer approved of our intent to continue in a direction away from the crowd and toward Professor Pichot's apartment further up the grade, where we visited for a while. He took me across the street to visit the stark interior of the pantheon shrine, and then directed me how to get back to my hotel. I followed his instructions and arrived without incident. But that wasn't the end of the day for me, although I never admitted the rest to Professor Pichot. I donned a windbreaker I imagined would make me look like a foreign correspondent, if only I had an arm band like they wore. I joined the excitement, marched down St. Germaine behind a student leader, who was being escorted for negotiations with

authorities, and got caught in a trap laid by police. I bravely lay down on the pavement with arms shielding my head as the police with rubber batons continued whacking students, right and left. I ended up at a glass enclosed café about a block above where students were burning a news stand on St. Germaine and stacking small foreign cars to block the entry of emergency vehicles. Police were responding with tear gas by then. From my vantage point inside the café, with another glass of wine, I watched something that changed the character of the Left Bank forever. It was students, with handkerchiefs shielding their faces from the tear gas, using iron bars to break up the bricks that surfaced the Left Bank street for use as stones to throw at the police. The streets have since been repaved with asphalt and riot police have retreated to large blue busses with windows shielded by iron grating, where they remain today. There is a quite different occasion I like to think of in my appreciation of Professor Pichot. He visited me in Galveston, and I recall his amusement at the Christmas decorations adorning palm trees on the boulevard into town. It turned out he had also been invited to visit NASA by the chief medical director, Charles Barry. I drove Professor Pichot from Galveston, and to my pleasure, was invited to join him on a guided tour around the NASA facility. We were met at the entrance by a large black limousine with red VIP flags on the front fenders and our auto tour ended at the NASA space museum. After examining successive early space vehicles that were on display and sitting in the driver's seat of the lunar-lander simulator to view the approaching moon surface, we started a tour of exhibits representing steps of the space program from earliest days. As a bonus for me, the first section of the exhibit focused on Sam the "space monkey" and featured several pictures of the late W. Lynn Brown, who was my graduate professor and the one who brought me with him to work at the Radiobiological Laboratory at Balcones Research Center near Austin. It was an emotional surprise to come such full circle from where I started as a graduate student at the Radiobiological Laboratory in Austin, Texas to that visit with Professor Pichot to NASA. Not many miles apart, but a lot of time.

TB: Could you tell us about your present interests and how they developed?

JO: I mentioned my doctoral degree was in General Experimental Psychology. That gives a person a rather broad background in different areas of scientific endeavor. From there, I followed where opportunities led for several years. Apart from my early participation in psychopharmacology clinical trials, where I was directed to provide support for statistical analysis and participate in

writing methods and results sections for manuscripts, I have been guided by the notion, “If it isn’t novel or controversial, it probably is not worth doing.” That has pushed me in the direction of controversy with authority or established practices on numerous issues. These included the use of least squares regression to produce tests of significance in unbalanced factorial designs that are comparable to tests produced by the same cross classification design with equal cell frequencies. Also, correcting for chance baseline differences in randomized or naturalistic treatment conditions, or conditions favoring the analysis of simple endpoint difference scores versus complete regression analyses for comparing treatment responses in repeated measurement designs. My present work is no less controversial, but to explain it really requires consideration of where it all started and of computer simulation methodology that has provided the criterion for evaluating comparative validities of different analytic procedures. My concern is with the development and evaluation of simpler methods for analysis from controlled repeated measurement designs that clinical investigators who do comparative treatment research can themselves understand. It has roots that extend back to my early work as a graduate student at the UT/USAF Radiobiological Laboratory, where I developed hands-on familiarity with classical repeated measurements analysis of variance. My work at the VA Central Neuropsychiatric Research Laboratory at Perry Point introduced me to problems for use of classical analysis of variance to analyze data from controlled longitudinal studies involving dropouts. My move to K-State University introduced me to FORTRAN computer programming, because there was no one else to do it for me in the open-shop computer environment there. That was the best educational experience I ever endured, and it was while I was supposed to be the teacher. If I do say so, I became expert in computer programming which, when I moved to the University of Texas, started me on the path to developing a series of increasingly powerful and flexible procedures for simulation of various conditions found in controlled longitudinal treatment studies. My introduction to correlation structures while studying multivariate methodology at the Psychometric Laboratory of the University of North Carolina, facilitated consideration of different patterns of correlated error when simulating realistic controlled clinical trials. Finally, my career-long close association with clinical researchers at different levels of experience and accomplishment, has given me unusual appreciation for the lack of preparation and motivation clinical investigators have when it comes to understanding the complex statistical modeling procedures increasingly promoted for analysis

of data in studies they design and conduct. My present concern is not with individuals who collect data on 6 or 8 patients, which are to be pooled into a large drug company sponsored study, but it is with the remaining clinical investigators who desire to pursue unique interests using sample sizes that are feasible to acquire in a reasonable time in local clinical settings. It assumes such investigators desire to understand a procedure that determines what they can legitimately conclude about results from their studies. My perspective is rooted in classical experimental design and analysis of variance I practiced laboriously at the Radiobiological Laboratory, while a graduate student at UT in Austin, in the mid 1950's. It was taught from a classic text authored by educator/psychologist Lindquist at the State University of Iowa. The text contained a major section on "mixed models" that developed the correct error terms and tests of significance for fixed and random effects in a variety of increasingly complex repeated measurements designs, using rather straightforward algebraic and arithmetic proofs. Simultaneously, a mathematical statistician name Eisenhart at the National Bureau of Standards in Washington, DC developed identical solutions using a more complex "components of variance" approach. The fact that later popular texts on experimental design and analysis of variance for psychologists and behavioral scientists, such as the widely used text by B.J. Winer, incorporated the components of variance approach indicates a deference members of applied disciplines tend to have for mathematical statisticians. As an empirical psychologist, relying on realistic simulation methods, I clearly do not share that problem.

TB: Are you suggesting you do not believe complex statistical modeling approaches are better than simpler approaches, which are better understood by clinical investigators who actually conduct most controlled treatment evaluation?

JO: I did not start out questioning the superiority of the mathematically complex statistical models and the equally complex maximum likelihood calculations. I am referring to tests of significance for differences in treatment effects in randomized repeated measurements designs that are based on Generalized Linear Mixed Models (GLMM), such as those produced by the SAS PROC:MIXED computer program, which has become so popular with statisticians working in the drug industry. No, my problem is that the GLMM procedure is not understood by clinical investigators who are responsible for executing, analyzing, and reporting results from comparative treatment evaluation studies in clinical psychopharmacology.

TB: If the mathematically complex statistical modeling procedures are not widely understood by the investigators in clinical psychopharmacology, are there procedures that you would recommend as an alternative?

JO: The approach I and a succession of collaborators has taken can be broadly classified as analysis of “summary statistics,” which combine observed repeated measurements into single composite scores that meaningfully represent treatment effects to be tested for statistical significance. It would be wrong not to recognize the frequent use of summary statistics by biopharmaceutical statisticians, as dependent variables for testing the significance of treatment effects in repeated measurement drug trials. Academic statisticians, such as Helena Kramer at Stanford Medical School, have published papers recommending such procedures for the analysis of “messy data” in less well controlled longitudinal studies. Analysis of covariance (ANCOVA) has been proposed by some as a way of correcting for missing data due to dropouts. The most commonly used summary statistic has been an ordinary slope coefficient fitted to the available measurements for each study subject. Simple and familiar tests of significance for difference between means of the slope coefficient are then employed to test the mean rates of change for subjects in two or more randomized treatment groups. A problem with most of the work that has been published on these procedures, and especially expositions related to the more complex generalized linear mixed model analyses, is they have provided worked examples or results from calculations applied to a single data set. Our contribution has been the use of simulation methods to evaluate how good the solutions really are.

TB: You have mentioned “simulation methods” several times in this interview. What are they in the context you use them?

JO: Simulation of clinical trials begins with generating raw data that looks like you would expect from an actual clinical study. The data generation involves use of an equation with coefficients, called parameters, which are controlled by the user to insert into the generated data you would expect to be made by fixed factors, e.g., treatment differences and effects of time in treatment, as well as random effects including sampling variability, carry-over effects, and random occurrences of missing data. When you print out the simulated data file, it should look like you would expect real data to look under the circumstances considered. If not, you have an opportunity to change parameters in the data generation equation and generate a new batch of simulated data that looks

more like you would expect. The advent of high-speed computers has made possible the use of simulation methods to evaluate and compare the validities of alternative statistical procedures. The procedures we have been interested in, test the significance of difference between effects of treatments, in a repeated measurements design, and in the presence of dropouts and autoregressive correlation structures for the simulated data. We refer to the simpler procedures as two-stage analyses. In stage 1, a linear slope coefficient is fitted to the measurements for each subject and weighted by the time the subject remained in the study before dropping out or completing the trial. Stage 2 involves application of common analysis of covariance, ANCOVA, to test the significance of the difference between group means with baseline scores and time-in-study entered as two linear covariates. High speed computation permits the whole procedure from independent data generation to tests of significance on the summary statistics to be repeated many times in relatively little time. The power of the test of significance is then estimated from the relative frequency of rejection of the null hypothesis across the series of hundreds or thousands of simulated data sets. Where the Type 1 error rate is to be calculated, no true treatment difference is introduced into the generated data that are analyzed. The accuracy of estimates of Type 1 error or power increases with the number of sample data sets generated and analyzed and can be as small as one considers important for comparing different analytic procedures.

TB: How satisfactory did you find this “simple two-stage analysis”?

JO: The first formulations of the simple two-stage analysis we evaluated did not weight the individual slope coefficients by time-in-study for dropouts, and the power of tests for differences in the mean slope coefficients was observed to drop off substantially as the frequency of dropouts increased in different simulated conditions. This was rectified by including weighting for time-in-study in the recommended analysis. Similarly, the value of more numerous repeated measurements was shown to decrease with increase in departure from a uniform correlation structure for the simulated data. In fact, the comparative results indicated that tests on simple difference between baseline and last measurement for each subject provided greater power than tests on slope coefficients fitted to all of the available measurements when the correlation structure of the repeated measurements was strongly autoregressive. By “strongly autoregressive,” I mean the correlations between measurements close together in time are much larger than the correlations between measurements further apart. Given that one considers the correlation structure of the

repeated measurements in choosing between a two-stage analysis of weighted slope coefficients fitted to all of the available measurements and a two-stage analysis in which simple difference scores replace the slope coefficients as the dependent variable for a familiar ANCOVA test of significance, we feel quite encouraged by the results for both Type 1 error protection and power.

TB: If I understood you correctly you prefer to use simple over complex statistical methods. Have you employed the simulation methodology to compare validity of the simpler and more complex procedures?

JO: We have done a number of comparisons under different simulated design, data structure, and dropout conditions. That is where we unexpectedly got ourselves in another controversial situation. We did not expect the simpler two-stage procedures to be superior to the “state-of-the-art” procedure for analysis of data from clinical trials with missing data due to dropouts. All that concerned us was that the simpler methods should not have seriously inferior validity. Monte Carlo runs of 1500 or 3000 simulated sample data sets with different correlation structures, linear or non-linear patterns of true mean change, and different random or non-random dropout conditions were generated, and each of the data sets was analyzed by both the simpler two-stage and more complex GLMM procedure. The simple two-stage analyses of both weighted slope coefficient and simple endpoint difference scores evidenced appropriate Type 1 error protection under all of the conditions examined, whereas complex “state-of-the-art” GLMM random effects model formulation using error structure specification, recommended by the author of the SAS PROC.MIXED procedure, revealed non-conservative error protection about half the time. More to our surprise, in no case where the more complex GLMM analysis provided appropriate Type 1 error protection was its power superior to that of a simple two-stage analysis, the choice of which was based on the error structure of the simulated data. Much of this work has been published or will, we hope, be published in good time.

TB: This is a good time to conclude the interview with Dr. Overall on an optimistic note.

JO: I’m afraid I have gone on much too long as result of my identification with clinical investigators, whom I believe are essential to the continued improvement in treatment of psychiatric disorders. The work we are doing now has proved quite controversial, and I appreciate the opportunity to call it to the attention of anyone who might be interested. The simple two-stage analysis still lacks an objective rule for choosing the number of measurements to include in the

research design or in the Stage 1 definition of change, even when more have been obtained. We continue to work on that, so please stay tuned.

TB: I would like to thank you very much, John, for sharing all the information about your life, education, and career.

JO: I hope we'll see one another again before too long, Tom.

47. GREGORY F. OXENKRUG

TB: We are in Waikoloa Village in Hawaii at the annual meeting of the American College of Neuropsychopharmacology. It is December 9, 2001. This is an interview with Dr. Gregory Oxenkrug⁴⁹ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Please tell us where and when you were born, something about your early interests, and education.

GO: I'm very glad to have this interview, and especially that you are my interviewer because it was your textbook and monographs I read first when I entered psychopharmacology. I was born 60 years ago, in 1941, in Leningrad, in the Soviet Union. It's now called St. Petersburg in Russia. During the Siege of Leningrad during World War II, it was my Mother who saved my life. There were only two kids on our street who survived.

TB: Could you say something about your family?

GO: My father was a pharmacist and almost all of my relatives, including my aunts and uncles, were doctors on both sides. I knew from an early age I would study medicine, and I was also dedicated to chemistry to the extent that in high school I took a college course in it. I was admitted to medical school at 17 and my interests were in endocrinology and genetics. Then, in the fifth year, I became intrigued with psychiatry, and attended all the lectures and rounds by Professor Khvelevetskiy at the Bekhterev Psychoneurological Institute.

TB: Who was professor Khvelevetskiy?

GO: Professor Khvelevetskiy came from a family of famous physicians, lawyers, and musicians. He was Chairman of the Department of Psychiatry at the Bekhterev Psychoneurological Research Institute and a very gifted psychopathologist.

TB: Were you involved in any research as a medical student?

GO: I was interested in fingerprints and would have liked to do some research on that under Professor Khvelevetskiy but he didn't let me.

⁴⁹ Gregory F. Oxenkrug was born in St. Petersburg (Leningrad), Russia (Soviet Union) in 1941. He graduated from medical school at the University of St. Petersburg. His first research position was in Institute of Endocrinology outside of Leningrad, and then, he moved to the Bekhterev Psychoneurological Institute where he obtained his Ph.D. and became a member of the faculty. He emigrated the U.S., and initially had a fellowship at Duke University Medical Center in Durham, North Carolina. Subsequently, he spent time at Boston University and the Massachusetts Institute of Technology in Boston, Massachusetts, until he joined the faculty in the Department of Psychiatry at Wayne State University in Detroit, Michigan. Next, he became a member of the faculty at Brown University in Providence, Rhode Island, followed by moving to a position at Tufts University, Boston, Massachusetts. He was interviewed in Waikoloa Village, Hawaii on December 9, 2001.

TB: How did you get interested in fingerprints?

GO: I was interested in genetics and learned that fingerprints are unique for each person; they are formed in the first trimester of pregnancy, and the pattern of fingerprints is different in schizophrenic patients than in normal subjects. I reviewed the literature and although Professor Khvelevetskiy liked my review, he did not want me to do research.

TB: Why?

GO: Because in 1948, the Communist Government closed genetic schools and many people involved in genetic research lost their job and, sometimes, freedom.

TB: So, you were not allowed to do genetic research?

GO: But Professor Khvelevetskiy liked my review; he used to call me “Mendel” and after my graduation from medical school in 1965, he tried to get for me an appointment in his Institute. But, his request was denied, mainly because I was Jewish and they did not want to appoint a Jew in a medical research position. Fortunately, in 1964, an Institute of Endocrinology was built outside Leningrad. It was a huge facility and I got a job as a senior technician in one of the laboratories. It wasn't a medical research position, but it made it possible for me to do some research and Professor Dilman, who was in charge of the laboratory, was a genius.

TB: What was his special field?

GO: Professor Dilman was very interested in the mechanisms involved in the aging process, and he had a unique theory that still holds up. He was the first to suggest that hyperinsulinemia plays a role in the etiology of cancer and high blood pressure and is one of the major mechanisms in the aging process. He published many books and some were translated into English. After he published his last book, he moved to the United States. Later on, he developed cancer and died about seven years ago in New York.

TB: Could you say something about your research in his laboratory?

GO: I was involved in studying the endocrine changes in breast cancer patients by measuring hormones in the urine.

TB: What did you find?

GO: The levels of estrogen-like compounds and cortisone remained high even after ovariectomy. In 1966, in collaboration with oncologists, I published my first paper on the findings.

TB: When did you move from the Institute of Endocrinology to the Bekhterev Psychoneurological Institute?

GO: In 1967. Slava Lapin, the Head of the Psychopharmacology Laboratory at the Institute was looking for somebody with experience in measuring cortisone and I was accepted in their three year Ph.D. program.

TB: Did you have any contact with Professor Khvelevetskiy after you joined the Institute?

GO: Very much. We worked in close collaboration.

TB: Could you tell us about the history of the Laboratory of Psychopharmacology at the Bekhterev Institute?

GO: It was the first psychopharmacology laboratory in the Soviet Union, established by Slava Lapin, in 1960, at the initiative of Professor Boris Lebedev who was Scientific Director of the Institute.

TB: Was this the Professor Lebedev who was later director of the Mental Health Unit of the WHO?

GO: Yes. He was Scientific Director, first, then the Director of the Institute, before he was appointed, in 1964, as an officer in the Mental Health Unit of the WHO. By the time I arrived he was in Geneva.

TB: He was the one who hired Slava Lapin to set up the laboratory?

GH: Yes. Initially the Laboratory was on the third floor of the building with animal quarters on the first floor. By the time I arrived, the Laboratory had eight rooms on the second floor, designated for pharmacological screening and behavioral pharmacology, and four rooms on the third floor for biochemistry. Lapin's first research collaborators were Rebecca Khaunina and Eugene Schelkunov. Then, Yuri Nuller, a psychiatrist, Irina Prakhie, a veterinarian, Maya Samsonova, a neurophysiologist, Irina Kiseleva, a medical doctor, and I joined the team.

TB: So your laboratory was in the Institute founded by Bekhterev. Could you tell us something about Bekhterev?

GO: Bekhterev was a very prominent neuropsychiatrist. He was professor and Chairman of Neuropsychiatry at the Military Medical Academy in St. Petersburg, established by Peter the Great in the 17th century. Among many other things, he did some work on conditioning, similar to Pavlov, who was a physiologist. There was some kind of strife between them; Pavlov would never

allow Bekhterev to become a member of the Russian Academy of Sciences. At age 50, Bekhterev had to retire from the Military Medical Academy and, in retirement, with private donations, he founded a Neuropsychological Institute. He was personal physician to the Czar's family, so they gave him the land where the Institute was built. At the time, the Institute was on the outskirts of the city, but now it is in the center of St. Petersburg.

TB: When was the Institute opened?

GO: In 1907. Then, in 1917, the Institute was taken over by the government of the Soviet Union.

TB: But Bekhterev stayed active, didn't he?

GO: He did, but apparently he dabbled in Stalinism and was poisoned with mushrooms in 1927. He was never officially condemned, but the Institute was converted temporarily into a hospital.

TB: So, Bekhterev was poisoned. What was the official report of his death?

GO: According to the newspapers, he was in Moscow, presiding over meetings, and went to a ballet, in the evening before he died at night. The rumor was that it was his second wife, who poisoned him on the orders of the KGB. But, as years passed, he was rehabilitated. By the 50th anniversary of the Institute, in 1957, the hospital became a Research Institute again with Bekhterev's ashes in an urn in the middle of the huge room he used as his study. They were buried in the cemetery next to Pavlov's grave. The burial was a big celebrated event but I guess

Pavlov wouldn't have liked it!

TB: Could you tell us about the research in the Laboratory?

GO: One of the ongoing projects was on acetylcholine esterase inhibitors, the antimuscarinic drugs, some of which were used as insecticides. This was well before my arrival. I understand the first compound Slava Lapin worked with was beta-phenyl-GABA that he called originally phenigama but was to become known as Phenibut. In the initial preclinical studies, Lapin conducted in collaboration with Rebecca Khaunina and Irina Prakhie, phenigama was found to have a similar pharmacological profile to meprobamate and diazepam. Then Khaunina and Maslova showed the substance passes the blood brain barrier. In clinical trials, conducted by Professor Khvelevetskiy, Phenibut was found to be an anxiolytic drug with hypnotic and antimanic effects. By the mid-1960s, the first paper on Phenibut was in print and a monograph was written by Lapin and Khaunina on, "The Role of GABA in the Nervous System." It was published by the Leningrad University Press.

TB: When you joined the Laboratory, in 1967, what was your first research project?

GO: Lapin and Schelkunov were interested in the mechanism of action of antidepressants. I was involved in endocrinological research before, so I was given two to three months to orient myself about the state of art in psychopharmacology, and especially, in antidepressants.

TB: Was any research going on in the Laboratory with antidepressants at the time?

GO: Yes. In 1964, Lapin published the first review in the Soviet Union on imipramine and Schelkunov was studying the role of cholinergic structures in antidepressant effects. By the time of my arrival, there was a battery of tests in use, developed by Lapin in collaboration with Schelkunov, Khaunina, Prakhie, and Samsonova, for screening potential antidepressants. By 1968, one year after my arrival, there was sufficient information to report the results of seven years of systematic research on screening for antidepressants.

TB: Where was it published?

GO: In Russian, in the Proceedings of the Bekhterev Institute under the title “Experimental Studies on Antidepressants.” The report focused on the fact that many screening tests, considered to be predictive of antidepressant effects, such as reserpine antagonism and amphetamine potentiation, are non-specific because they confound sympathomimetic action and stimulation of motor activity with antidepressant effects. Many drugs, including amphetamines, cocaine, and anticholinergics are active in these tests without necessarily having mood elevating effects in depressed patients.

TB: In 1969, Lapin and you published a paper in the Lancet that turned attention to the role of serotonin in the antidepressant effect of drugs.

GO: The title of our paper was, “Intensification of the Central Serotonergic Processes as a Possible Determinant of the Thymoleptic Effect.” We followed up our first paper, in 1970, with another entitled “The Frog as a Subject for Screening Thymoleptic drugs.” Apparently, the frog brain contains predominantly serotonin (5-HT) whereas the rodent brain contains predominantly norepinephrine (NE); Lapin found in frogs that reserpine’s sedative effect was potentiated by tricyclic antidepressants, instead of being reversed in rodents. Subsequently, we also found in rodents, like rats, it was L-DOPA and not L-hydroxytryptophan that antagonized reserpine induced sedation, while in the frog, it was 5-hydroxytryptophan and not L-DOPA that potentiated the sedative effect of reserpine. Our results corresponded with Arvid Carlsson’s finding that in rats,

one could prevent reserpine-induced sedation with L-DOPA, but not with 5-hydroxytryptophan. It was mainly on the basis of these findings we assumed the mood-elevating effect of antidepressants is related to serotonin. It eventually led to my appointment as Director of a Biochemical Laboratory in the Laboratory of Psychopharmacology. We had the capability to measure 5-HT in brain tissue as well as the uptake, and inhibition of uptake, of 5-HT in blood platelets. About that time, we proposed to use the “frog test” in screening for potential serotonergic antidepressants in the Soviet Union. Our proposal was rejected by the Soviet equivalent of the FDA. Our paper was also rejected by the Russian psychiatric journal. Our request to publish our “serotonin hypothesis” in the January issue of the *Lancet*, in 1969, was, however, approved by the Ministry of Health, after a lengthy delay by the KGB.

TB: What about Carlsson’s paper?

GO: It was published a few months later.

TB: So, your paper with Lapin was published first?

GO: Yes. This whole area of research was opened up by Lapin’s findings that imipramine did not reverse but potentiated the sedative effect of reserpine in frogs. After that we conducted a series of studies in frogs.

TB: Was it you who carried out those studies?

GO: Lapin did the first study, which showed imipramine potentiated the effect of reserpine in frogs and my task was to find out why. A major part of my Ph.D. Thesis dealt with the “frog.” It was my finding that frog brain contains mostly serotonin and has no noradrenaline or dopamine at all. In reserpine reversal by tricyclic antidepressants in rodents, what we actually saw was that the effects of the noradrenergic system mask those of the serotonergic system. But, in the frog, you can study pure serotonin effects. About that point in time, a pharmaceutical company in Switzerland developed a drug that in rodents showed antidepressant effects but did not seem to work clinically. We tested the substance in frogs and found it did not work as an antidepressant; it had a strong noradrenergic effect without any serotonergic properties. Based on the findings of our test, it was clear the substance had potent noradrenergic effects, but, without serotonergic properties, it was not antidepressant. Our paper in the *Lancet* was very well received; it ended up as a citation classic. Our hypothesis was frequently referred to as the “serotonin hypothesis of depression,” which we formulated prior to publication. In our hypothesis, the emphasis was on the

role of serotonin and tryptophan in the mechanism of action of antidepressants and not on the etiology of depressive disease. The two may or may not be related.

TB: Did the work with serotonin continue in the Laboratory after these two important publications?

GO: Yes. Simultaneously with our research, Samsonova, in our laboratory, was studying the pharmacology of the antidepressant effects of tryptophan. Serotonin, as you know, is a metabolite of tryptophan, and Lapin became interested in kynurenine, another metabolite of tryptophan.

TB: Is the “frog test” still in use for the screening of potential antidepressants?

GO: I think the “frog test” was used in the identification of both zimelidine and fluoxetine. But, in Finland, a researcher found it works in winter but not in summer. In summer, you have to keep frogs in the refrigerator for a couple of weeks and then you can work with them.

TB: You said that it was not introduced in screening for antidepressants in the Soviet Union. Why?

GO: I suggested it for screening in Russia but a very prominent psychopharmacologist told me not to do it, and he would not help me because, “I don’t want to be accused of promoting mental depression in the frog.” It was the same fear from 1948 to 1950, when the Communist Government closed genetic and physiological studies.

TB: Before leaving Russia what else did you work on?

GO: I worked with serotonin uptake in platelets and with the dexamethasone test, especially in alcoholics. We found alcohol did have an effect on serotonin uptake similar to antidepressants and that the escape of cortisone from suppression after the administration of dexamethasone at midnight is not present in all depressed subjects but is also present in other psychiatric diagnoses.

TB: In spite of the restrictions, it seems you were in contact with many psychopharmacologists in the West.

GO: I went to the library regularly and asked colleagues for reprints from the West. Professor Lapin established and maintained contact with Western colleagues. We had many guests in the Laboratory, including Sam Gershon, Joseph Knoll, and the late Jerry Klerman. We also actively corresponded with Bill Bunney, Barney Carroll, Arvid Carlsson, Alfred Pletscher, and Bernard Brodie. Merton Sandler’s and Irv Kopin’s visits left an indelible mark on my life.

TB: So, in 1979, you left?

GO: I arrived in Boston, in December 1979, and was invited to Duke University, in Durham, North Carolina where Prof. Schanberg was kind to offer me a postdoctoral position for two years,

with the understanding I would get my medical license. I told him I would be happy to work as a Ph.D., but he strongly suggested getting my M.D. Professor Schanberg remained my guardian angel for many years and chaired the credentials committee of ACNP in the year I was accepted as a member. From Durham, I went to Boston, and from 1980 to 1982, I was a clinical Associate Professor at Boston University and a postdoctoral associate in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology. In Boston, it took me a year to get my medical license. Just about that time, Sam Gershon moved from New York to Detroit, to become Chairman of the Department of Psychiatry at Wayne State University, and Lapin wrote him about me. So I applied and spent six years with Sam. They were the happiest years in my career and during them serotonin was at the center of interest in the U.S.

TB: We are talking from about 1982 to 1988?

GO: Yes. Many of the things we did in Leningrad were redone here but with much better techniques. By that time, we also knew that both serotonergic and noradrenergic mechanisms could be involved in the mechanism of action of antidepressants. It was in those years I became interested and involved in research with melatonin. I remembered from my research in Leningrad that, after injecting frogs with reserpine, the animals lost their righting reflex and then started twitching. As a third step, we saw a yellowish-brown discoloration in their skin. It was not until I came to the United States that I realized the discoloration was the result of melatonin and, if you give melatonin to a frog, you get this discoloration. I started to think about the role of melatonin in the serotonin-norepinephrine balance and hypothesized it might be melatonin that's responsible for the antidepressant effect of drugs. To prove our hypothesis, I collaborated with a fellow Sam hired in Australia, Dr. McIntyre. He was a very talented chemist and we found that administration of melatonin has similar pharmacological effects seen with antidepressants. Then, after we demonstrated that clorgyline, a MAO-A inhibitor, stimulates melatonin production, Dennis Murphy and his group at NIMH became involved in studying the effects of selective MAO-A inhibitors in monkeys, and we became involved in studying the same drugs in humans.

In addition to stimulating melatonin production, MAO-A inhibitors also decrease blood pressure. We were the first, in 1985, to prove the hypotensive effect of MAO-A inhibitors is mediated by melatonin. About ten years later, melatonin's hypotensive effect became a very popular object of investigations. We then found the hypotensive effect of MAO-A inhibitors was

mediated not only by melatonin, but also by its immediate precursor, N-acetylserotonin. Furthermore, we found not only melatonin, but also N-acetylserotonin, behaves as an antidepressant in some pharmacological tests. I started to study the pharmacological properties of N-acetylserotonin and found it prolonged life in mice. Then, we showed it decreases lipid peroxidation and production of tumor necrosis factor-alpha. So, the focus of my research moved from serotonin through melatonin to N-acetylserotonin.

TB: Are we still in the 1980s, while you were in Detroit?

GO: Yes. Then, in 1988, Sam left, and I was invited to Brown University to become a Professor of Psychiatry there. So I moved to Providence, Rhode Island and spent six years there. Then, in 1994, I moved to Boston to become Professor of Psychiatry at Tufts University and Chairman of Psychiatry at St. Elizabeth's Medical Center, a teaching hospital of Tufts University.

TB: It seems that during the years your activities shifted from pre-clinical to clinical. Did you do any clinical work in Russia?

GO: Some, but I was never an attending physician, except for the first years when I was in endocrinology. I was doing some clinical research in the Laboratory of Pharmacology with MAO-A inhibitors, tryptophan, and worked with alcoholics. After my arrival in the United States, while in Boston, I worked for two years as an attending psychiatrist in a State hospital. My position with Sam Gershon was looking after patients on the inpatient unit, and only in my spare time, after regular work, would I go to the laboratory because that was not what I was paid for. At Brown University, I was Chief of Psychiatry at the VA Hospital and seeing outpatients.

When I was appointed Chair to the Department of Psychiatry at St. Elizabeth's Medical Center, I gave up clinical work because I couldn't do everything. I inherited a residency program that was on probation and I had to attend to that immediately.

TB: How many residents do you have?

GO: Twenty. Clinical work today requires a lot of paper work and it wouldn't be proper use of my time.

TB: You said in Detroit you were in a clinical position.

GO: Right, but I also had an NIMH grant to study the dexamethasone test in Alzheimer's dementia. By the time I left Detroit, we already had one paper published in *Psychiatry*. What we found was that only in women was there a correlation between the DST test and the clinical state.

I would have liked to follow up those findings in Providence but at the VA hospital, we only had male patients. So my grant was terminated but we got another from the VA to study the effects of benzodiazepines on melatonin and cholesterol, because benzodiazepines have a significant effect on lipid metabolism.

TB: What is your current research?

GO: We're studying the effect of N-acetylserotonin on aging. We found that it prolonged life in male but not female mice. These are long-term studies; it takes about two years to do them because one has to wait until all the mice die. We found that N-acetylserotonin decreases the oxidation of lipids and, recently, we started to study the possible antioxidant effect of some of its analogues.

TB: Any other research project you did or are currently doing you would like to talk about?

GO: We used light therapy for winter depression and also tried it in narcolepsy. We are participating in the CATIE project that is a very interesting project I feel very good about.

TB: Could you tell us something about the CATIE project?

GO: It is a multi-center comparative study, in which some of the new antipsychotics are compared with some of the old ones.

TB: How many centers are involved?

GO: Thirty-five centers; all in the United States.

TB: Are all new atypical antipsychotics included in the study?

GO: We are using risperidone and olanzapine.

TB: What about the old drugs?

GO: Trilafon. But this is not just another comparative study of old and new drugs; we are also studying the effects of social factors on treatment.

TB: Who is the principal investigator of the project?

GO: Jeffrey Lieberman. The project is supported by a NIMH grant.

TB: Is it a placebo-controlled study?

GO: No. It's a double blind, parallel group design. It's a long-term study; patients who fail to respond to treatment in the first phase are moved into the next phase.

TB: What dosages are used?

GO: We have flexible doses with an upper cap.

TB: What would you consider your most important contribution to the field?

GO: The serotonin studies we conducted in the Laboratory of Psychopharmacology.

TB: Your early work?

GO: Yes, my early work because it attracted attention on the role of serotonin in the mechanism of action of antidepressants and stimulated research. I don't want to take full credit myself, of course, for that work. I also think the recognition of the role of melatonin in the action of antidepressants and that the antidepressants effect is related to their acute pharmacological action and we don't need to give them beyond two weeks to get optimal effects.

TB: Are you saying the duration of a clinical trial with an antidepressant should be no longer than two weeks?

GO: What I am saying is that we are dealing with an acute pharmacological action and not with chronic effects on receptors. If I fly from Boston to London, at the time I arrive in London my endogenous system is still "on Boston time" and would not produce melatonin until my endogenous cycle became adjusted. If I give an antidepressant that stimulates melatonin production, it would help the endogenous cycle to synchronize with the new environmental day/night schedule. In our studies, we found that for the first four nights after arrival, there was no melatonin production, and then it started up gradually. But, if you give melatonin in the first two nights, you help the transition. I see the pathology of depression as a product of the endogenous cycle of melatonin and antidepressants as substances that help correct it. This might not be the case in all types of depression; some patients relapse, despite taking antidepressants for years.

TB: You don't think prophylactic therapy is necessary?

GO: Not the way it's done now. We need to follow patients, check them with regularity, and give them antidepressants when they need them. An effective way to use antidepressants is by infusion, but American psychiatrists are not familiar with it. In Europe, it is widely used and within two hours of starting the infusion, some patients are symptom free. When we stop the infusion, the depressive symptoms re-appear and we need to repeat the infusion until the patient remains symptom free.

TB: Did you use antidepressants IV yourself?

GO: I did, in collaboration with Prof. Khvelevetskiy.

TB: Do you have any research grant to study antidepressants?

GO: I have some industrial support.

TB: So you are currently running a clinical department of psychiatry?

GO: Right. But I also do basic research and teaching.

TB: What was the last paper you published?

GO: It was on the effect of N-acetylserotonin on aging.

TB: Did your research interest shift from depression to aging?

GO: Aging and depression have a lot in common, physiologically. In 1979, Dilman, Lapin and I published a chapter on, "Serotonin and aging" in Essman's five volumes *Serotonin in Health and Disease*.

TB: So, your research in aging is a continuation of your research in depression?

GO: Yes.

TB: How did you get involved with ACNP?

GO: Sam Gershon invited me to the annual meeting in 1982, and, since that time, I probably haven't missed any of the meetings.

TB: When did you become a member?

GO: In 1999. I'm very proud of being a member. The annual meetings of ACNP are the best meetings I attend.

TB: Are you active in the College?

GO: I'm trying to be; I was on a committee and have presented papers and posters at annual meetings.

TB: Am I correct you are involved in clinical trials as well?

GO: I spend about two days weekly with clinical trials.

TB: Where do you get the patients?

GO: From the community.

TB: Is there anything else you would like to add?

GO: No, I think we covered more or less everything.

TB: Thank you very much for sharing this information with us.

GO: Thank you very much.

48. STEVEN MARC PAUL

TB: This will be an interview with Dr. Steven Paul⁵⁰ for the archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the College in Hawaii. It is December 12, 2001. I am Thomas Ban. I think we should start at the very beginning; if you could tell us when and where were you born and something about your education?

SP: I was born in Chicago, Illinois on November 2, 1950, so I am just 51 years of age. I grew up on the south side, in a suburb of Chicago, 25-30 miles south of the city. My family was born and raised in Chicago and I went to grade school and high school in a town called Flossmoor, south of the city. I struggled a bit in high school but was very interested in playing rock and roll music. I played drums in a band every weekend. During my junior and senior years of high school, I started to get interested in science and took advanced placement biology. I'm not sure how I got into it frankly, because I was a pretty average student. I did well in that course; it's interesting how teachers play a very influential role in your life. I also worked in the office of a pediatrician. His name was Dr. Sullivan and I also worked with a Dr. Goldberg, my family pediatrician, who took me under his wing. I did urinalyses, eye tests, and a bunch of different things in the office. It was a lot of fun and I even sutured a few lacerations. He took me on rounds at the hospital and for a high school kid that was pretty impressive. I went to my high school college counselor and I said I wanted to be a doctor and he replied we're going to have to figure out a way to get you into college. So, I went to Tulane University, in New Orleans, and it was an interesting experience because I had never been in that part of the country; I didn't even know where New Orleans was. I became a pre-med at one of those southern undergraduate colleges. You were at Vanderbilt, so you know Tulane and Vanderbilt are very similar. I decided to study hard and become a doctor. So, like all overachieving pre-meds, I worked hard and got very good grades and applied to medical school after only two years of undergrad. I got into Tulane medical school and a couple of others, but I elected to stay at Tulane. I went, thinking I was going to be a surgeon, and took

⁵⁰ Steven Marc Paul was born in Chicago, Illinois in 1950. He received his M.D. degree from Tulane University in New Orleans, Louisiana, where he began residency training. He continued his residency at the University of Chicago and the Intramural Research Program of the National Institute of Mental Health in Bethesda, Maryland, where he also completed postdoctoral training in neuroscience. After rising through the ranks at NIMH, he was recruited by Eli Lilly Pharmaceuticals in Indianapolis, Indiana for an executive position. He was interviewed in Waikoloa, Hawaii on December 12, 2001.

Gross Anatomy the summer before I went to medical school so I could be a teaching assistant in my first year of medical school. That was a horrendous experience. Having to work day and night in the anatomy lab in New Orleans in the summer was just too much. I decided that was probably not the route to go, but I connected with a very unusual psychiatrist. You probably know him, Bob Heath.

TB: I do.

SP: Bob was an extremely dynamic, charismatic person. He was a student of Rado at Columbia, a psychoanalyst, although he was more of a surgical type. He worked on the Greystone project, one of the early programs to look at subcortical regions of the brain and their functions. These were the years people didn't know exactly what each brain region did. I spent time following Bob around; it was unusual for a young student to be interested in the brain. I went to the operating room with him, while the neurosurgeon he was working with was putting depth electrodes in various brain regions. It was fascinating and amazing; nobody will ever do those experiments again. Bob would interview these patients just like we're sitting in a room now, and up on a screen would be the EEG of the amygdala, the hippocampus, the cortex and, when you invoked certain emotions during the interview, you'd see the amygdala go zoom, zoom, zoom, just like that. Of course, Bob had lots of theories about what brain functions were subserved by the different regions. He was a very energetic and passionate guy. He approached science very much like a physician. He didn't really test any hypotheses. He knew the right answer. He knew the cause of schizophrenia and it didn't matter what the data said, he knew. But he had an enormous impact. He was a very charismatic guy, a tall handsome man all the women loved, who had five kids, a big house and a big farm; just a fascinating character. We could spend an hour talking about Bob Heath stories. He was incredible, one of the youngest chairmen of psychiatry in the country, about 30 years old, when he came from New York to New Orleans and got involved with Huey Long and all the other funny stuff in New Orleans. Some great Walker Percy books were written about Bob's kind of character. So he really got me excited about the brain. I met another person you know well from down there, Don Gallant, he and I became very good friends.

TB: I know Don, of course.

SP: Don was a wonderful mentor. I often regret not telling Don how good a teacher he was. He cared about his students, cared about them deeply, and had an enormous impact. The two of them

were very different, in terms of style, and what they provided, but both were extraordinarily impactful on my career. That was a very important formative period and I knew when I was a first year medical student, I was going to go into psychiatry and neuroscience. I met another student, with whom I became very good friends as a freshman. She was the oldest student in the class, who came to medical school at 38 or 39 years of age, and I was the youngest in the class. She worked with Arnie Mandell in California, and before that with Jonas Salk, she was Salk's technician. She was also good friends with Julie Axelrod. And she told me, you know Steve, if you want to be a scientist, you should go work with Julie Axelrod. Well she had me go work with Arnie Mandell for a summer or two. So I went to La Jolla and followed Arnie Mandell around. He was a wonderful, energetic mentor and I don't think I've ever met anybody quite as bright as Arnie Mandell, with an incredible, incredible mind. In the few months I was there, I did some research. We looked for this enzyme, N-acetyl-transferase in the brain and N-acetyl serotonin, which I think to this day, is an important enzyme, even if not as well studied as many of the other enzymes. And we published some work just from the few months of work I did there. I spent a really impactful summer in Julie Axelrod's lab at NIH that was unbelievable. Julie had just won the Nobel Prize and I had the bench right next to his desk. Joe Coyle was there and Roland Ciaranello was in the lab. Just a remarkable group of people, and all of Julie's boys would go to lunch every day with him and that was very exciting. I knew then, I was going to come back to NIH, but I had to finish medical school. In my senior year, I bumped into Danny Friedman. Danny came to New Orleans and we had lunch at Antoine's. He recruited me to be a resident at the University of Chicago. I graduated early from medical school, did six months of neurology internship at Charity Hospital in New Orleans, and then went to the University of Chicago as a psychiatry resident. We had a small class. Bob Freedman, who is in Colorado, was in the class and a bunch of very good people. It was a very exciting department in those days. Herb Meltzer was there and Heinz Kohut, the analyst, Bob Schuster and many others. A tremendous department Danny had pulled together, a small but extraordinarily fine department. I worked with Danny in the lab and a couple of other of his people, including Angelos Halaris and Herb Meltzer. We worked on some deaminating enzymes that were responsive to LSD; and Herb and I, in that one year, published five or six papers. I also worked with him on effects of neuroleptics; we looked at prolactin levels at the Illinois State Psychiatric Institute where Herb was, although he was

affiliated with the Department of Psychiatry at the University, as well. I spent a wonderful, wonderful year there and became very close to Danny Friedman. He was sort of my psychiatric father. I had such wonderful mentors, Bob Heath, Don Gallant, and Danny Friedman. Then I went to Julie Axelrod's lab; but if I ever needed advice on anything, I would call Danny. I was in Axelrod's lab for a couple of years and worked on two projects. The first was on the metabolism of estrogen and the formation of catecholestrogens. These are dihydroxy catechol derivatives of estrogen, the result of P450 enzymes that were thought to be only present in the liver, but we showed the brain also had a P450 enzyme that metabolized estrogen to catecholestrogens. That was the project I worked on with Julie and we showed that metabolic pathway for the first time. Then I started work, while still in Julie's lab, on GABA receptors. After two great years in the Axelrod laboratory, I went over to Fred Goodwin's lab, and finished my clinical training so I could become Board certified in psychiatry. I also began my independent research career working in Fred Goodwin's branch.

TB: Are we in the late 1970s?

SP: Right. I got a little lab, a couple of modules in Building 10, a couple of floors above Julie's lab. I became involved in some clinical, but mainly basic research. That lab grew and grew until Fred became the Scientific Director of NIMH intramural program and I became a lab chief with Candace Pert and John Tallman. They were independent investigators who had their own sections, while I had mine. I continued to work on three or four different projects defining the role of GABA receptors and the mechanisms of action of benzodiazepines. The three really noteworthy contributions I made with my collaborators in those years was that we pinned down that benzodiazepines worked through the GABA receptor systems, that barbiturates, particularly the anesthetic barbiturates, worked through this GABA system, and provided very good evidence that ethyl alcohol produced much of its sedative and anxiolytic effects, through the GABA_A receptor. We developed some microsome preparations to demonstrate this and found some imidazo benzodiazepines could block the effects of alcohol. We had a couple of very highly visible papers. Finally, one of the contributions I'm most proud of is that we described some metabolites of progesterone, allopregnanolone, as well as one of the mineralocorticoids, and showed that these steroid hormones, instead of interacting with the classic nuclear steroid hormone receptors, interact with a GABA receptor. We called these neuroactive steroids, which have become a very

interesting area of research. These steroids can be made in the brain de novo or progesterone can get into the brain from its peripheral sources. In animals, there is a significant amount of progesterone made by the adrenal gland, and after entering the brain when metabolized, it produces these sedative, hypnotic, antianxiety steroids. We described this in a Science paper in 1986, and it became one of the more highly cited papers of my career. One of the exciting things that happened about a year ago was that, based on the citation count of the ISI, in the last 20 years, I was one of the top 50 most cited neuroscientists. This is a very exclusive group of people; Sol Snyder, Arvid Carlsson, and Paul Greengard are among them. So, I was very pleased.

TB: Can we go back to clarify the chronology of events? You became lab chief in the mid-1980s.

SP: Right.

TB: And you were a very active chief and did several important projects.

SP: Yes, a couple of very interesting things which are relatively unknown about my career, but something I'm proud of, is that I had a clinical and a preclinical program. We did clinical research in schizophrenia. I worked with a number of very good clinical investigators at NIMH. We started imaging studies, tried to image the benzodiazepine receptor, and also, using cerebral blood flow techniques, to look at the effects of benzodiazepine receptor agonists and antagonists. We did a lot of in vivo imaging in animals to set the stage for these studies. We studied the patients both in the affective disorders arena and in schizophrenia. So it was an extraordinarily broad research program I led. In retrospect, I probably worked on too many problems, but it was fun. I have an attention deficit disorder when it comes to science!

TB: This was around the time the receptor assays came about, right?

SP: Exactly. So we used those assays and discovered a number of new receptors for the dopamine transporter. We did studies on the binding of tricyclic antidepressants to the serotonin transporter, and Sal Langer published a wonderful paper in *Nature* showing, "An Imipramine Receptor in the Brain." We found, Sol would hopefully verify this, that imipramine could be labeled with tritium and bound to the serotonin transporter.

TB: It seems that we skipped some of your early contributions. The first paper of yours I read was with Don Gallant.

SP: We did some work with Don on a couple of things. I did a review article with him on the cardiotoxic effects of tricyclic antidepressants, and Don was a very scholarly person, so we

published that in a book. We studied some schizophrenic patients and gave them Deanol, which supposedly was a cholinergic type drug in the brain. Bob and I published a paper together on trying to map pathways from the cerebellar vestibular nucleus to the forebrain. He had some notions about the cerebellum, and today I think some of his ideas have turned out to be pretty correct.

TB: Didn't you do some work also in immunology?

SP: We did some immune work too. I got back into that at NIMH, looking for immunological stigmata in schizophrenics, and we found some interesting things. We never could quite pin down whether they were related to schizophrenia, but we did publish some nice papers on that.

TB: Let's get back to the work at NIMH you were talking about.

SP: One of the other things I did at NIMH, which was unusual, and maybe a result of the times and salaries, was I started to see patients. If you look at my career, you'd say this is a guy who has principally done research, but for a good 15 years, I had a fairly significant practice of psychiatry. I had a home office, and saw patients virtually every Saturday, Tuesday, and Thursday evenings. These were principally depressed patients, but I also had a few schizophrenic and bipolar patients I saw in combined psychotherapy and pharmacotherapy. In those days, Washington was populated principally by very good analysts, but not very good or comfortable prescribing medications, like lithium, neuroleptics, or antidepressants. This was before the SSRI's were even introduced, so a lot of tricyclics and monoamine oxidase inhibitors were used. I practiced a bit with Fred Goodwin and saw a bunch of VIP's from time to time. In fact, Nate Kline sent me a bunch of patients. Way back, I worked on some folks in sort of consultation with Frank Ayd. So this goes back quite a few years, but I learned about clinical psychiatry from practicing it, being out there, and confronted with problems year in and year out, day in and day out. I was a good clinician.

TB: I suppose this was in the 1980s.

SP: It was. I was a lab chief, from 1984 to 1988, and it was probably one of the better periods of my career. I won, in one of those years, the Efron Award from the ACNP, one of the better awards I received. We had just published all the alcohol work, the neurosteroid work, the imipramine binding and serotonin transporter work. A lot of that came out at that time. We were labeling imipramine binding sites on platelets and studying patients, so we had a paper in the *Archives* around then. I had some tremendous postdoctoral fellows. One great thing about being at NIH was the number of young, bright people you could attract to your laboratory. It was extraordinary,

and I was blessed to have maybe 50, 60, 70, or 80 postdocs come through my lab. Many of them are doing very well right now; they are professors, chairpersons of various departments of psychiatry or pharmacology in this country and throughout the world. So things went pretty well. Then, in about 1988, or so, Fred Goodwin left and became director of ADAMHA. Herb Pardes had departed from being NIMH Director and Lew Judd came. When Lew Judd was the NIMH Director, I was fortunate to have been appointed Scientific Director of NIMH. That was an interesting and challenging job. I was now the director of the program I entered in 1976, as a postdoctoral fellow in Axelrod's lab, and Irv Kopin was our lab chief. And this was the program that Seymour Kety built back in the 1950's. Seymour Kety was, in my view, one of the great psychiatric scientists of our time. Seymour came back from Boston to the intramural program in his 90s, while I was Scientific Director. He had a little office and came in while he was working on his Danish adoption studies. We had eight, nine, or ten members of the National Academy of Science, and we had Lou Sokoloff, who won the Lasker Award for developing the deoxyglucose brain imaging technique. Didn't you, around the 1980s, do some work with SSRI's?

TB: We did.

SP: We did a lot of work labeling serotonin transporters and showing that was where the SSRI's worked. So, 1988-89 was kind of a tumultuous time at NIMH. We were trying to make some changes, to introduce a peer review system, and for me, as an administrative person, it was pretty stressful. For a lot of my friends and colleagues, the Bob Posts, the Phil Golds, the Dave Pickars, and the Danny Weinbergers of the world, really good people, this was stressful, trying to introduce a peer review system and to raise the bar on the quality of science. The blessing of being in the intramural program of NIMH is that you are not reviewed. You are free to do things without having to write research grants and tell people what you're going to do. That's a wonderful thing, but it comes with some liabilities.

TB: Would you like to mention a few of those who were in your program?

SP: They were extraordinary people. In the clinical program we had Dennis Murphy, Judy Rappaport, Bob Post, and Danny Weinberger.

TB: Could you say something about them?

SP: Judy is probably the premiere child psychopharmacologist and psychiatrist in the world. Bob does wonderful work on kindling and bipolar disorder. He helped to introduce the anticonvulsants

as treatments for bipolar disorder. Tom Ware is a very thoughtful, very bright circadian rhythm person. Richard Wyatt, Danny Weinberger, and Joel Kleinman all worked on schizophrenia. Pickar was in my group and Trey Sunderland did a lot of great things in aging. David Rubinow did work on premenstrual syndrome, whatever they call it now. It was an extraordinary group of scientists. Without a doubt it was the premiere clinical program. Preclinically, in the basic neuroscience laboratories, they were also wonderful people. Julie was still very active. Lou Sokoloff, I've mentioned; Julio Cantoni and Seymour Kaufman were there. We had a fellow that you probably know, Howard Nash, a great geneticist. Mike Brownstein was there. We had a great systems neuroscience program with Mort Mishkin, Bob Desimone, and Leslie Ungerlieder. This was a very fine program.

TB: It looks like a comprehensive program. Did you have a central theme you focused on?

SP: That's an interesting question. We really didn't do that. I inherited a program; it sort of evolved the way it did in terms of the players. We never had a vision of where we wanted to go, and to be honest with you, as grateful as I was to have ended up in that program, my one frustration was that I couldn't figure out a way to make it greater and to continue to make it grow. One of the issues is how do you do that? I think they are starting to do some really good things now. Dennis Charney has joined the intramural program at NIMH, but I don't know if we ever quite recreated what Seymour Kety did. Now, of course, it's different. When Seymour was there, there was nobody to start with. He set it up de novo, had all this space and everybody came.

TB: How did it start? Could you say something about that?

SP: I hope you have Seymour Kety's tape. I hope you got him before he died, because he was an extraordinary figure. Seymour has told this story, and I don't know if I can do it justice. In those early days, the intramural program of NIMH and the intramural program of NINDS, the neurologists, were one entity. It was a wonderful program. There was a bunch of very good people, and it was a great place. It's still a fine place, but it was always a frustration to me that I couldn't make it better. I was 38 years old when I became Scientific Director. That's pretty young to have all this.

TB: Were you the youngest Scientific Director of the program ever?

SP: I'm sure I was. I don't know how old Seymour was, but certainly of recent times, I was the youngest.

TB: Seymour Kety was probably older than you when he became director.

SP: He was at Penn for a while before and at different places. I did that job for five years and enjoyed it. Frankly, I never thought I would leave NIMH. I thought I would probably be carted off in a box one day from my laboratory but in a rather uncertain career move, I visited Lilly. They asked if I wanted to oversee their neuroscience research program. Lilly introduced Prozac in 1987; so this was in 1992. Prozac had been a very successful drug. They had a few other interesting drugs, and were investing heavily in neuroscience research and psychiatry, which was a bit unusual for a Midwestern pharmaceutical company who made its reputation primarily in insulin for diabetes and antibiotics for infectious diseases. So, I went there and probably shocked a few people in making that career move. It was the end of 1992 that I announced I would resign my position as Scientific Director and move to Lilly; and I did so in March 1993. I was very fortunate. The people at Lilly were very good people, had a fine program in neuroscience and still have to this day. We're probably one of the most competitive, if not the most competitive, company. We were just about to launch olanzapine, Zyprexa. I did that job for about three years, and then, was asked to oversee all the different therapeutic area research programs, including infectious diseases and oncology.

TB: Everything, not just psychotropics?

SP: Yes, and I recruited my successor, Chris Fibiger from Vancouver, who is now the Vice President of Neuroscience. Many of the vice presidents in the other areas, I also recruited. I continue to this day to have a laboratory and my own postdocs and technicians.

TB: What are you working on in your laboratory?

SP: I have been working on Alzheimer's disease for the past five years and that is going very, very well. I am pleased with the work. We've been trying to figure out the genetics of neurological disorders. It's incredible what's happened in the last ten years; there are some really important genes! For a symposium this week, we invited Peter St. George-Hyslop from Toronto, a fantastic scientist, who discovered two of the early onset presenile genes. But I've been working on a more common gene called apolipoprotein E, particularly the E4 allele, which is associated with risk for Alzheimer's disease; if you have one copy of this gene from either your mom or your dad, you have a threefold greater risk of getting the disease. If you have two, one from your mom and one from your dad, so you're an E4 homozygote, you have a ten to twelvefold greater chance, and you

get it early. So 50% of people who'll get Alzheimer's disease at age 65 are E4 homozygotes and 90% by age 85. So this is a very important gene for increasing your risk for Alzheimer's disease, relative to the more common E3 allele. The question is how it does it; so we've done most of our research in transgenic animals. We've genetically engineered animals to express these different genes and have found they facilitate amyloid deposition. So, that's been a big project.

TB: Any other important projects?

SP: The other big project we've been working on that is very exciting, is on this whole notion of being able to vaccinate against Alzheimer's disease. I don't know if you've heard this story, to vaccinate against the α - β peptide that forms amyloid in your brain. It's a small 40 to 42 amino acid peptide that deposits in the brain of patients, who have Alzheimer's disease and forms plaque. This is what Alzheimer, who was a psychiatrist, first described, in 1907. These are plaques he saw and they consist mostly of an aggregated fibrillar form of this peptide. What we and others have found is that antibodies can be raised to the peptide and even though these don't get into the brain very much, they can reduce the deposition of the peptide in forming amyloid plaques in transgenic mice. So this is a wonderful opportunity to test the amyloid hypothesis of Alzheimer's disease.

TB: Are the brains Alzheimer worked with preserved?

SP: I don't know the answer to that. Alzheimer was an interesting fellow. And here's a funny coincidence; Lilly bought Alzheimer's house!

TB: In Munich?

SP: It's not in Munich. It's a modest size home. When we bought it, fixed up everything and dedicated it, there was his microscope. So I have a picture of me looking into Alzheimer's microscope. It's in his house, not the Alzheimer Museum.

TB: So, there's an Alzheimer Museum too?

SP: At the hospital. During the dedication I had lunch with one of his daughters.

TB: That's very interesting.

SP: Yes. I think it's his youngest daughter. Alzheimer didn't live to be very old; I think he was a smoker or something. Anyway, I've been working on Alzheimer's disease which, in this country, is considered a neurological disorder. Interestingly enough, in Germany, it's still a "psychiatric" disorder and psychiatrists usually take care of it. In the US, it's mostly neurologists, geriatricians, and some psychiatrists.

TB: You moved in your research from receptors to genetics?

SP: Absolutely, genetics, exactly! When I was at NIMH, before I left, I started a project in collaboration with Ed Ginns, a genetic epidemiologist, studying the genetics of manic depressive illness, in the old order of Amish in Lancaster. Now, this is an interesting story. In 1987, there was this wonderful paper published in *Nature* purporting to claim there was a genetic locus on chromosome 11, 11p15 on the short arm that contained a gene for manic depressive illness in the Amish. This was published by Janice Eglin. There was a very famous geneticist named David Houseman. Probably for a year or two, it was probably the most exciting and interesting finding in psychiatry. In that region of the genome, there were two interesting genes. One is the gene for tyrosine hydroxylase, which, as you know, is a gene that makes catecholamines and the other is for tryptophan hydroxylase, which makes serotonin. So Ed Ginns and I thought these must be the genes for manic depressive disease. So, we first cloned tyrosine hydroxylase and compared it in some Amish folks that had manic depressive illness and couldn't find any difference. This was a very curious finding, so we ended up repeating the linkage findings. One of the interesting things about doing genetic studies with DNA, is you can study the exact same subjects repeatedly. In the years we were measuring urinary catecholamines, you could never get those patients again. They were gone, and you certainly couldn't study them at the same time. But for genetic studies, I take your DNA, I take your lymphocytes and I transform them. I make lymphoblasts and store them. I can grow them and they are a continuous source of DNA. So, all of this DNA was stored in a repository in Camden, New Jersey, and you could order it. So, we ordered the DNA from these subjects and repeated the linkage analysis. To make a long story short, we didn't get the same results. So, we published another paper in 1989, "Failure to Confirm," and this was a very interesting because the group that originally published this consisted of extraordinarily competent, honest, good scientists. So, I approached the group and I said let's work this out together. We ended up publishing a paper in *Nature* with the original authors of the other paper. To this day, people think we were the ones who wrote the original paper. The sample Janice Eglin worked with was phenomenal. She's got families, pedigrees, seven, eight, nine offspring, three or four of which had manic depressive illness. Fantastic! We began to collaborate with Janice, and to this day, we still do some work. It's been a little less intense since I've gone to Lilly, although I'm starting with the new genetic techniques, the SNP genotyping, the single nucleotide polymorphism gene

typing, to sequence the human genome. Now that we have all these genes, we can go into regions we think are important and find the genes one by one. We had a paper that came out two or three years ago, in *PNAS*, which Seymour Kety sent in for us because he was a member of the National Academy. What we did in this paper was we looked at the Amish and carried out what's called a linkage analysis, where we put genetic markers, spaced throughout the genome, to see if there were markers that seemed to be segregating with the transmission of bipolar disorder in the subjects. If there's a marker that seems to be linked with the illness, you can say a gene might reside there. Then we did an interesting thing. We flipped the linkage analysis around statistically and asked whether or not there was any relationship to being mentally well in these pedigrees. In other words, was the absence of affective disorder linked to any marker and sure enough, we found a region on 4p15, where there's evidence, not unequivocal, but some evidence for a gene that conferred mental wellness. It was a protective locus. What's interesting about that is, remember the apo E gene I told you about, well it comes in three flavors, E4, E3, and E2. E3 is the most common variant, present in about 85% of the population. About 15% has one E4 gene that makes you three times more likely to have Alzheimer's disease. If you have two, that's ten times. Well it turns out that the E2 gene is protective. So if you inherit one E2 gene, you have a 50% lower risk of getting Alzheimer's disease and if you get one E4 from mom and one E2 from dad, the bad effect of the E4 is blocked by the good effect of the E2. You see where I'm going?

TB: Yes.

SP: So this concept that we have alleles, forms of genes that can confer disease or disease protection, is the concept we're seeing more and more now for all the complex traits we're interested in. Is that going to be interactional? You get an interaction and the difference, by the way, between the E4 allele, the E4 gene and the E2 gene, is two amino acids. Just two amino acids makes you go from having a tenfold greater risk to having one-half the risk, so a twentyfold change in the risk for getting Alzheimer's disease. How does that work, that's what we're trying to figure out.

TB: Weren't you also trying in your research to bridge receptorology with molecular genetics, working with cell lines and trying to profile drugs to receptors? Could you talk about that?

SP: That's an exciting area because once the molecular biologists got into receptor biology, the whole field took off. A good example, and this is not so much my own work, but work we've

done or capitalized on at Lilly, is that if you take serotonin, and serotonin has 15 separate receptors that have been cloned from different genes, what you can do is take the complementary DNA or cDNA for each of those and you express them separately in a cell line and use the cell line in screening for drugs. You can come up with drugs that are specific for a particular type of serotonin receptor, either one that stimulates or one that blocks it. It has been used for glutamate receptors, dopamine receptors, or just pick your set of receptors. It's a wonderful, powerful approach to discovering new drugs.

TB: So that's a kind of receptor screening for new drugs?

SP: Yes, absolutely. Some people call it rational drug design. I don't know what irrational drug design is. But the point is that if you go back to how we discovered imipramine, it was by accident. How did we discover chlorpromazine? It was by accident. It was done by astute, empirical observations. You modified chlorpromazine and you didn't get an antipsychotic, but you got a mood elevator. Or you're working on antihistaminic compounds and you come up with chlorpromazine, it seems to have antipsychotic effects.

TB: What about MAO inhibitors?

SP: They were discovered almost by accident, looking at the antituberculous MAO inhibitors and they seemed to have mood elevating effects. Didn't Nate Kline make some empirical observations?

TB: And George Crane, and others, even before that.

SP: But a generation of psychotropic drugs was created empirically, if you also think of John Cade's work in lithium. It was in the 1950's and 60's, when these drugs were introduced. So in 50 years we've gone from having no understanding of how the drugs work, before we were able to delineate the neurochemical mechanism of their mode of action. When it was shown that imipramine and amitriptyline block serotonin reuptake, the question was, could that be how these drugs work as antidepressants? Voila, now you come up with the serotonin transport inhibitors. Right?

TB: Right.

SP: And you have this new generation of SSRI's but it's now known that the noradrenaline carrier is important and combining those two, the serotonin and noradrenaline carriers, gives you a better antidepressant. It's also known that it's not necessarily the primary neurotransmitter effect that occurs acutely but it's probably the effects of the second and third messengers in gene expression

after you give the drug. So when I give a drug to your brain, it may up-regulate or increase serotonin in your synapse and that's going to cause a change in gene expression; it's probably those genes that are changing the protein products that are penultimately responsible for the drug's effects. Now we can use that information to discover brand new drugs that work better.

TB: How will things go? Do you need better feedback from psychiatry, or would this work by itself to generate the development of more selective drugs?

SP: That is a very interesting question because one of the things I think has gone wrong, is we've taken a lot of the empiricism out of psychopharmacology. In my research group at Lilly, the CNS program that Chris Fibiger heads up, they're discovering drugs that work on a whole variety of different receptors, glutamate receptors and serotonin receptors, and we have theories of what these drugs are going to do. But until you get them into people and good psychiatrists make observations, you don't really know what you've got. We've found, for example, that we bring a drug into the clinic for this or that disease and find it may not work; but look what else it does. That's what we need more of in psychiatry.

TB: But the current psychiatric nosology works against you because the diagnostic categories are too broad and pharmacologically too heterogenous.

SP: We're probably getting close to the etiology of Alzheimer's disease because we know what gene produces the disease. We don't have that yet in psychiatric disorders.

TB: I think in Alzheimer's, we might be closer than in other psychiatric disorders, but even in Alzheimer's, it will probably be better to restrict the concept to the original and look for the genetics of the early onset disease.

SP: The apo E gene is the late onset gene but there's a point you're making that's important. Even so, when does early Alzheimer's start? There's another syndrome called mild cognitive impairment (MCI); this is the big buzz word. It's a precursor to Alzheimer's, but I think people are depositing amyloid much earlier.

TB: The point I was trying to make was that by separating early onset from late onset disease we might get more homogenous populations.

SP: Well, I think that we have a much better understanding of the genetic etiology, pathogenesis, and pathophysiology of Alzheimer's disease than we do for schizophrenia or bipolar disorder.

TB: I think that's correct.

SP: In Alzheimer's disease, there are three amyloid precursor protein mutations, Presenilin 1, Presenilin 2, and apo E that have been described. These are actual genes, and we can show their importance in populations. In schizophrenia, we have certain regions of the genome identified, but no genes yet. My point is, if you think of the treatments for schizophrenia or for depression, to some degree, we're not going to go anywhere unless we get a drug that treats the etiology. The etiology of schizophrenia may have been way back in the second trimester of pregnancy, so you may be dealing with something that you can't treat etiologically in the adult.

TB: Absolutely.

SP: So there's still value in looking at things syndromically and saying, what is depression or cognitive impairment in schizophrenia and can we treat those? The treatment of schizophrenia started out in the 1950's by trying to treat the positive symptoms of psychosis, hallucinations and delusions. Right?

TB: This is what most people say but an early report on treatment by Sol Goldberg, based on the NIMH collaborative study, shows that the symptoms we refer to today as "negative symptoms" are the ones which responded specifically to antipsychotic phenothiazines.

SP: But the focus in therapy for years and years was, can you block the positive symptoms and was that enough? Then people started saying you can only treat these positive symptoms with certain types of drugs, but the patients remain impaired. Then we had this concept of negative symptomatology. Actually, who coined the word dementia praecox?

TB: Kraepelin by adopting Morel's term, "démence précoce."

SP: I've got a picture of Alzheimer and Kraepelin sitting in the same room in Munich. So what was Kraepelin picking up on dementia praecox?

TB: First, in 1893, he used it as a diagnosis that accommodated three syndromes: Hecker's hebephrenia, Kahlbaum's catatonia, and dementia paranoides, that he himself described.

SP: The point I'm making is that across history, people were picking out different parts of the syndrome we call schizophrenia. Today we think of it as a syndrome whose manifestations may differ from patient to patient.

TB: In the last edition of his textbook, Kraepelin himself described 12 different outcomes in patients diagnosed as dementia praecox.

SP: But you know, like Alzheimer's, like many diseases, you can get different etiologies producing the same phenotype. Like in Hodgkin's disease, the same gene is producing a different phenotype. Until we find something etiologically that we can put our fingers on in schizophrenia, it's going to be hard to get the nosology right. You see what I mean. Otherwise, you're just looking at symptom complexes and making theories, which are great, but you've got to come back and test them. For the time being, if you have a patient with schizophrenia you may be treating different symptoms in the syndrome, possibly with different drugs or combinations of drugs, like we do with cancer and many other diseases.

TB: Right.

SP: So we're working on drugs that might help memory disturbance, cognitive disturbance in schizophrenia, or on drugs that might be more effective for negative or positive symptomatology. I think you can approach the problem that way. In fact, if you want to do it properly, there is no other way. For the next ten years of my career, I'm probably getting back to schizophrenia on a new project that involves genetics but I'll also work on some of these Alzheimer's disease therapies.

TB: Would you like to say something about the research you intend to do in schizophrenia? SP: There are some exciting new clues on the genetics of schizophrenia that have to do with stemline mutations in spermatozoa. Another very exciting paper presented a pathway involved in the production of an amino acid, which Sol Snyder has worked on a lot that seems to be very involved in receptor function. Those are two interesting clues to etiology or, if not etiology, to pathophysiology, although we don't have, at this point, a lot of data to support a hypothesis.

TB: But currently your research is focused on Alzheimer's?

SP: Mostly on Alzheimer's, right.

TB: Do you have any drugs in the making for Alzheimer's?

SP: Yes. In the Alzheimer's area, we've got a drug that I helped discover that was approved just a week ago and will go into the clinic, if all goes well, by December of this coming year.

TB: Any other interesting drugs?

SP: We've got a couple of others, too. We're working on neuroprotective strategies for Parkinson's disease. But a lot of my drug discoveries are vicarious through the efforts of the

program and we've got many exciting, different types of drug candidates, going into the clinic. Not directly out of my laboratory but out of our whole program at Lilly, and that's exciting to me.

TB: You still seem to keep very close to CNS drugs?

SP: I do, but I have to worry about the other areas too, and I enjoy the fundamental breakthroughs going on in cancer, cardiovascular research, and infectious diseases. Fortunately, we have very good people who are experts in those areas, who I bring together into groups, and that's a nice challenge and a great opportunity.

TB: You mentioned a number of people you worked with at NIMH. Would you like to mention a few you trained?

SP: The folks that have come through my lab; some have done very well, a couple at this meeting, Shelly Schwartz who's at Duke, Leslie Morrow who's at the University of North Carolina, Steve Doetsch who's at Georgetown, Howard Gershenfeld at Texas, Aaron Janowsky is in Portland, Oregon, Paul Berger is at Cincinnati. I've been very fortunate with the folks who have come through my lab.

TB: It seems you have been very fortunate to work with interesting people. You were lucky with your own mentors.

SP: They were very varied people; they each brought different things to the mix, from a fellow like Bob Heath, to an Arnie Mandell, a Don Gallant, a Danny Friedman, a Julie Axelrod and Fred Goodwin. I've been very fortunate to have worked with some great people.

TB: Would you like to say something about your publications?

SP: Going back in time, I think the alcohol-GABA work was good, the neuroactive steroid work, the allopregnanolone work; a lot of papers were good, including the original binding studies with the GABA-benzodiazepine complex and the barbiturate work. All those are solid pieces of work. Recently, I'm very proud of the Alzheimer's work we've done, the transgenic mouse model and some of this new work on the antibody over the past couple of years, the antibody to the α - β peptide. Those are the pieces of work I think are the most important.

TB: What is your last publication?

SP: The last paper I had, came out a few weeks ago in the *Proceedings of the National Academy of Science (PNAS)* demonstrating that a semi-synthetic tetracycline called minocycline has neuroprotective effects, it works in the animal MPTP model of Parkinson's, and not by its

antimicrobial properties, but through what we think is a brain anti-inflammatory property. That's a very interesting, provocative paper. We have a couple of others in press or submitted that I'm also pretty excited about. One, in transgenic mouse models, could be used for determining how much amyloid is present in the brain, by measuring how much alpha and beta antibodies are present in the mouse blood.

TB: For your contributions, you were the recipient of several awards. Would you like to mention just a few?

SP: The Efron Award of ACNP is a great award I received. The Distinguished Service Medal from the US Public Health Service, the Arthur Fleming Award, and the APA's Research Award were all exciting awards. The Max Hamilton Award of the CINP was a nice award, as well as The Bennett Award from the Society of Biological Psychiatry.

TB: When did you become a member of ACNP?

SP: I joined the ACNP, in 1982. This really is a fantastic organization. I've come to virtually every meeting for 25 years. I've served on Council twice and served as the President, in 1999. That was a great honor. I've served on the Credentials and the Program Committee. So I've been fortunate to do a lot of things for the organization, this College.

TB: Is there anything you would like to add that we have not covered?

SP: I think it's a great College. When I was President, one of the things I wanted to do was figure out a way to keep it intellectually vigorous, to make sure that we were bringing in the young, the brightest people, so we continued to evolve and wouldn't become extinct. We've done some good things along that route. I'm very pleased with the quality of the new members and the Fellow promotions. It's a great, great organization.

TB: Just one more question. What are your thoughts about the future of the field and the College?

SP: The field is going to be as good as the science we produce. To comment more on psychiatry because I'm a psychiatrist, we've gone from an era where it was hard to even know anything about nosology, to know anything about disease processes. Clinicians that came into the field were not as interested in applying rigorous scientific methods to understanding what was going on. It may have been such an overwhelming problem, but I think we've made a lot of progress in 50 years, and we will continue to apply sound scientific methods to tease out the genetic and the non-genetic factors for diseases. What's the etiology? What's the pathophysiology? What's going on in the

brain that causes signs and symptoms of disease and then treatment interventions will occur at the various stages, like all other diseases. Fundamentally, we'll understand the brain that is the most complex organ in the body. But it's not going to be easy to understand soon, although we've made extraordinary progress, and this College has done a remarkable job as a catalyst.

TB: That's a reasonable note on which to end this interview. Thank you very much.

SP: Thank you, Tom that was fun. Great!

49. EUGENE S. PAYKEL

TB: This will be an interview of Professor Eugene Paykel⁵¹ for the archives of the American College of Neuropsychopharmacology. We are at the Princess Hotel in Acapulco, Mexico. It is December 11, 1999. I am Thomas Ban. Let's start from the very beginning: where and when were you born and brought up?

EP: By origin, I am a New Zealander, although it has been many years since I have lived in that beautiful country. I mainly am English but have affiliations to many parts of the world. I was born in Auckland, New Zealand and my father was a businessman who had been a student at Harvard and met a young concert pianist from New York, whom he later married and who is my mother. I was educated in Auckland, New Zealand and I went to medical school in what was then the only medical school in New Zealand, Otago University in Dunedin. I was born in 1934, and I was a medical student from 1951 to 1956. After two years as a house physician in Auckland, I had the wanderlust, like many New Zealanders, and I got on a cargo ship to England for further training. I am one of the past generation able to make that journey, half-way across the world, as a ship's doctor for free passage. So I was ship's doctor with a crew of seventy and twelve passengers crossing the Pacific Ocean, through the Caribbean and up to New York where we spent a week at port in Newark before crossing the Atlantic in winter to London. I spent a few years training in internal medicine in England, which was a common pattern in those days for young ambitious British psychiatrists who wanted to work in the best teaching centers.

TB: When did you start training in psychiatry?

EP: In 1962, I started as a resident at the Maudsley Hospital, London. I was there for three years as a resident and for one further year. That was a very stimulating environment, particularly in those days. The Professor was the late Sir Aubrey Lewis who was a rather austere and forbidding man on the outside but quite warm on the inside. The number of bright stimulating young people were working there was phenomenal. I was blessed with highly stimulating contemporaries and

⁵¹ Eugene S. Paykel was born in Auckland, New Zealand in 1934. He received his medical training at Otago University in Dunedin, New Zealand. He trained in internal medicine in Auckland, New Zealand and in London, England and in psychiatry at the Maudsley Hospital, London. Subsequently, he was a research fellow in the Department of Psychiatry at Yale University School of Medicine in New Haven, Connecticut. After research training at Yale, he returned to England for a faculty appointment at St George's Hospital Medical School in London. He subsequently moved to the faculty of Cambridge University. He was interviewed in Acapulco, Mexico on December 11, 1999.

an environment that encouraged critical thought and academic development. Still infected with wanderlust, in 1966, I crossed the Atlantic to Yale University in New Haven to undertake research. That turned out to be a very fruitful time. I stayed almost five years, got married to my English girlfriend and our first child was born a few months before we returned home to England, in 1971.

TB: With whom did you work at Yale?

EP: With Jerry Klerman, and I was very fortunate I chose him and that he chose me. We set up what became the Depression Research Unit at Yale. It started with a small grant from NIMH and gradually increased. I was responsible for hiring, with his approval, Myrna Weissman, starting what became one of the most glowing marital partnerships in American academic psychiatry.

TB: Could you say something about the research you did at Yale?

EP: We undertook a variety of studies in depression and this was the start of my own research career. We were interested in classification of depression which, at that time, was a widely published topic and still the subject of controversy, centering on the distinction between endogenous and reactive depression but also involving other aspects. An off-shoot of that was a cluster analysis, one of the early applications of that technique in psychiatry. On a sample of one hundred and eighty five depressives, who had been studied in great detail, we were fortunate to gain access to a new cluster-analytic classificatory program which ran on one of the most powerful computers in existence, an IBM 360. The program took some hours to run at night but it would run today on a desktop computer without any problem. The object was to explore the classification of depression using a technique that was more appropriate than the factor analytic techniques which had been used so far. Factor analysis produces dimensions of variation, but we wanted to find groups of subjects. It turned out well and we identified one psychotic group and three non-psychotic groups which could be called neurotic. One group was characterized by anxiety with depression and a chronic history, another by hostility, and a third group of young people with fluctuating depression and a background of disturbed interpersonal relationships. Perhaps the most enduring aspect has been the demonstration that what had been regarded as a single group, neurotic depression, was rather diverse. Since that time, usage of the term neurotic to describe depressives has dropped out of the literature. A second study was of the relationship of life events to depression.

TB: Could you tell us about the kind of information your analyses were based on?

EP: This was a comprehensive set of information on a diverse group that included detailed clinical characterization of patients based on about thirty-five symptoms derived by the Clinical Interview of Depression, elaborated from the Hamilton Depression Scale. In addition, there was information on history of onset, previous history, neuroticism on a scale called the Maudsley Personality Inventory, devised by Eysenck, which has stood the test of time, and a Life Events Interview, which we designed ourselves as a semi-structured schedule to characterize events at the onset of depression with precision. That led to the more expanded life event work. It seems difficult to appreciate now, but at that stage, the issue of whether life events played any role in the onset of depression was hotly disputed. There were two schools of thought; one regarded all depression as constitutional and biological and would admit no room for life stress; the other school emphasized psychological factors, whether recent or in early upbringing but was not prepared to admit a place for constitutional or genetic factors. The only way to cut through this problem was to undertake proper empirical studies. We were fortunate that a large epidemiological study with more than nine hundred subjects from the general population was being carried out by the sociology department. I was able to incorporate in that study the same life events interview we used for the six months prior to the clinically defined onset of depression in our study. Analysis showed clear differences in event occurrence between our depressed patients in the six months prior to onset and the general population controls, matched on social characteristics. Prior to onset of depression, there were more events, and particularly, certain kinds of events, characterized as undesirable or “threatening.” Also, prior to depression, there was an excess of events that involved an exit from the social field, a sociological concept involving a departure of somebody, creating one kind of loss. That was the first published study looking at comprehensive life events by a careful interview schedule prior to the onset of depression compared to matched controls. It was my first citation classic!

TB: What year?

EP: 1969. The title was, “Life Events and Depression,” published, in the *Archives of General Psychiatry*. It received a lot of attention at the time. That was preliminary to a second study aimed at a psychopharmacological question. By the later sixties, the antidepressants had been available since the late 1950s and there was good controlled trial evidence for considerable benefit in the acute treatment of depression. The common pattern of using drugs was to treat for three months,

since that is the way we treat many acute disorders, but not to continue the antidepressant. But, clinically, it was becoming apparent there were high relapse rates. It was not yet conclusively shown whether that was due to pharmacological withdrawal from the drug or whether psychological factors could have been important since cessation often heralded discharge from care of a psychiatrist. So, we designed a controlled trial that would treat patients acutely with amitriptyline for two months. Those who responded were assigned randomly either to continue the antidepressant for six months, or to withdraw double blind onto placebo. A third group withdrew onto no medication, since that is the natural situation in a clinic. We also decided to enrich the study by incorporating a group on psychotherapy. We settled on case-work orientated individual therapy by social workers. It was a form of therapy that later became Interpersonal Therapy, although that was not a term we used then.

TB: Who else besides you and Gerry was on the research team?

EP: By that time, Myrna Weissman and Brigitte Prusoff, a statistician, had joined the group. So, the study was turned into a six cell factorial design, drug versus placebo versus open withdrawal, with or without the psychotherapeutic modality that later became Interpersonal Therapy. Like all such studies, it took several years. Long-term trials are also long term tasks for the investigators!

TB: What did you find?

EP: The findings were clear-cut. Continuing antidepressant treatment was beneficial in preventing relapse. Relapse wasn't entirely abolished, but it was better than halved by continuing antidepressants for six months. There was no difference between withdrawing to placebo and withdrawing to no medication, so placebo effects were not important and this was undoubtedly a drug effect. The psychotherapy had no effect on relapse, but it did have an effect on improving social function and interpersonal relationships by the end of the study. There was a synergistic effect in that medication prevented relapse and the psychological treatment improved relationships and function. The best outcome was to receive both. That has been my belief ever since, which will not surprise you. So, that was the culmination of the Yale studies. We had by that time, launched a large series of studies on life events and other psychiatric disorders. We looked at the treatment of suicide attempters and we studied other themes as well, but I returned to England, with my wife and our four months old child, to an appointment at St George's Hospital Medical School in London.

TB: So from Yale you returned to London and worked at St George's Hospital Medical School.

EP: That medical school has a very interesting history. It developed, as most of the London medical schools did, in the late eighteenth century; Jenner, the pioneer of vaccination had been a student. Hanging in the library is the skin from Blossom, the cow from which Sarah Nelmes, the milk maid, contracted cow-pox having been protected against smallpox. After two or three years, in which I was still heavily involved with the Yale studies, I embarked on my own research program. Still interested in depression type and treatment outcome, I started work on MAO inhibitors. There had long been an interest in whether the MAO inhibitors benefited a particular group of depressives.

TB: Were they considered to be particularly effective in atypical depression?

EP: That view came from William Sargent, a charismatic clinician, not a researcher, at St. Thomas' Hospital in London, and people who worked with him. They coined the term "atypical depression" to describe a type of depression they felt, on clinical grounds, showed the best response to MAO inhibitors. It was characterized by anxiety, increased appetite, increased weight, and increased sleep, as opposed to the typical insomnia and loss of appetite that occurs with other types of depression. What underlay this was the idea it wasn't endogenous depression and was, therefore, not typical. I was fortunate to obtain an American grant from NIMH to undertake a controlled double-blind trial of phenelzine versus amitriptyline versus placebo, in a sample of outpatient depressives and mixed anxiety depressives at St. George's.

TB: What did you find?

EP: The findings of that study were that phenelzine was surprisingly effective and comparable in efficacy to amitriptyline. When we looked at subjects benefiting particularly from one drug or the other by comparing drug versus placebo differences, it was subjects with anxiety, in addition to depression, who showed selective benefit from phenelzine. That was one of the findings supported by a number of other studies in the literature, including studies of panic disorder.

TB: What assessment instruments did you use?

EP: A wide variety of clinical ratings. We used the Hamilton Scale, our own Clinical Interview, the Hopkins Symptom Checklist self-report version, and the global clinical impression of severity and improvement. Also, we collected quite a lot of history data, and made an attempt to classify or sub-classify depression on the basis of some short definitions within that outpatient spectrum.

TB: In what doses did you use the drugs?

EP: They were what I would describe as standard British doses, amitriptyline one hundred and fifty milligrams daily and phenelzine sixty milligrams daily. The more predominant view in the eighties and the nineties has been that increase in appetite and increased sleep characterize MAO inhibitor responders. To some extent that is true, but evidence regarding anxiety in Sheehan's excellent study, suggests some anxious patients benefit preferentially from MAO inhibitors over tricyclics. In those days, we did not have available the serotonin reuptake inhibitors which also seem to benefit patients with anxiety more. Subsequently, I became interested in milder depression in general practice. By this time, we were getting into the early eighties. An active question, both in Britain and worldwide, was whether the antidepressants benefited the milder depressions treated in primary care. In Britain, in those days and since, only about one in ten patients with depression are referred to a psychiatrist and nine out of ten are treated by general practitioners. In most countries, including the U.S.A., the majority of the treatment of depression is not from psychiatrists, but internists and other kinds of physicians. Often, depression in general practice is milder and we had no evidence, in spite of widespread use of the tricyclics, they were beneficial in those milder depressions. Particularly, we had no evidence as to any characteristics that might distinguish patient gaining benefit from the antidepressant from those who were not. So we undertook a controlled trial of amitriptyline versus placebo in general practice in a wide area of south London. I was fortunate to have as collaborator Professor Paul Freeling, a very eminent figure in academic general practice in Britain. We enrolled more than twenty general practitioners, who agreed they would identify patients with depression that we could interview and randomly assign double blind to amitriptyline or placebo. The target dose of amitriptyline was one hundred and fifty milligrams daily and the median dose was one hundred and twenty five milligrams daily, a little lower. Subjects received six weeks double blind treatment and then assessed by a psychiatrist again, with the same standard rating scales. There were clear cut results, which surprised us.

TB: What did you find?

EP: Amitriptyline was considerably superior to placebo in mild depressions. The mean Hamilton seventeen item total score at inclusion was a little below fifteen, so the majority of patients would not have satisfied the inclusion criteria in standard studies assessing new antidepressants in

psychiatric outpatients. We looked at the group showing benefit of drug over placebo and those, for whom drug was no better than placebo. Over a wide variety of characterizations, there was no selectivity, except in one respect, and that was initial severity. Patients with major depression, probable or definite, on the Research Diagnostic Criteria, showed clear superiority of drug over placebo. Patients with minor depression did not. When we characterized subjects further on the initial Hamilton scores, we found in patients who scored below thirteen, the drug was not superior to placebo but in those patients with scores of thirteen and over it was. The maximum scores were in the mid-twenties. There seemed to be this clear severity threshold, which extended a little below major depression, but did include the more severe end of minor depression. That took me to the mid-eighties.

TB: When did you move to Cambridge?

EP: In 1985, having been a full professor at St. George's, I moved to Cambridge to succeed Professor Sir Martin Roth as head of the department, the equivalent of chairman of psychiatry in Cambridge. My first few years were heavily engaged in administration and building a department rather than research. I had been undertaking at St. George's, in collaboration with the department of pharmacology, a series of platelet receptor binding and neuroendocrine studies, looking at receptor sensitivity in depression. We carried those on in the first few years at Cambridge, but not beyond, because the results had been largely negative. I was becoming disaffected with the platelet as a mirror of the brain. Although in the late seventies and earlier eighties, it had been attractive since it shares some of the receptors and the uptake mechanism for serotonin with the brain.

TB: Didn't you also get involved in epidemiological research in the elderly?

EP: I undertook some dementia epidemiology. There were strong epidemiological collaborators in Cambridge and we carried out large scale studies of elderly subjects in the general population. One study was of two thousand subjects aged over seventy five at the time of inclusion. That is a cohort which was started from 1985 to 1987 by a young Australian, who was working in Cambridge, Daniel O'Connor, which we kept going. The survivors are still being studied thirteen to fourteen years after the original study. They are a smaller group now because they were all over 75 at the time of the first study. We found rates of dementia, probably Alzheimer's, though you can't be sure in community studies, with incidence rates which doubled approximately every five years in age, reaching high rates in subjects over 90. There was not a hard and fast borderline

between mild cognitive impairment and more severe dementia in the older groups; it was more like a continuous distribution. It looked as though the clear cut separation we find in younger people, between those who have Alzheimer's and those who don't, began to get fuzzy in old age, suggesting a more continuous process. That has linked with brain banking work. We were fortunate that the brain bank started by Iversen and Bird in Cambridge was transferred with MRC funding to the department of psychiatry. With that, and with the help of a very creative research nurse, we were able to work with families and get their agreement to post mortem studies, so some of that is still going on. It has extended to molecular biology as well as neuropathology.

Meanwhile, I returned to my primary interest, which was depression, and in the late eighties we decided the important theme was longer term outcome and what to do about it. It had become apparent from the NIMH collaborative study by Keller et al., the studies by Lee and Murray at the Maudsley Hospital, and the study by Kiloh in Sydney, that the longer term outcome, which we had assumed would be good, was not. There was good controlled evidence that long term treatment on a continuation or maintenance basis, either with an antidepressant or lithium, cuts down markedly rates of relapse and recurrence in affective disorder. On the other hand, naturalistic follow up studies found high rates of relapse and recurrence, in spite of the availability of these treatments. So, the broad question, at the beginning, was what was the explanation? There were several possibilities. First, was the time delay that inevitably elapses when undertaking long term follow up studies. It was quite possible that relapse and recurrence rates in patients treated in the 1970s did not apply to patients receiving treatment in the 1980's and 1990's. Our first study was a prospective longitudinal follow up of patients being treated in Cambridge, in about 1990. The psychiatric services in Cambridge were fairly representative of the U.K. Although it is a high powered academic center, it has an ordinary general population, and the standard British National Health Service services. So, we followed people with depression, from their first symptoms, every three months up to fifteen months, or to earlier remission, and then for a further fifteen months to look at relapse. All subjects had major depression at inclusion and the majority had been hospitalized.

TB: What did you find?

EP: We found good rapid remission, as we had suspected, and only a small proportion not reaching remission by fifteen months. But we then found that in the fifteen months after remission, forty

percent of patients relapsed to another major episode, which was very much what earlier follow ups had found. The fact this was occurring in the 1990s did not make a difference. The strongest predictor of relapse was the occurrence of residual symptoms at the time of remission. We had set a broad criterion for remission, which allowed presence of residual symptoms rather than complete freedom; subjects who had Hamilton (seventeen items) total scores of eight or more were responsible for a large portion of the relapses. There was a seventy-six percent relapse rate in those subjects, as opposed to a twenty five percent for subjects in complete remission. We had some data about treatment received in this naturalistic study and, as near as we could establish, neither occurrence of residual symptoms nor the occurrence of relapse were related to failure to deliver treatment; subjects with both adverse outcomes tended to receive more rather than less antidepressant. That's the way it should work in good clinical practice. Psychiatrists, being rational, give more treatment to patients doing badly. So, it did not suggest failure to give treatment was the key issue.

We undertook a second study designed and targeted to collecting detailed data on the treatment actually received, subsequent to the acute episode. That had not been well studied before. There had been a number of studies, in general and psychiatric practice, showing failure to deliver good dosages of antidepressants in acute treatment, but it had not been studied beyond the acute episode. Again, ours were hospitalized depressed patients with ten percent of the sample bipolar depressives. We followed them at eighteen months after discharge and undertook a retrospective reconstruction of all treatment received and the evolution of symptoms over that period.

TB: How many patients did you have in your study?

EP: We studied a hundred subjects and the relapse rate was about the same as in the previous study. The intriguing finding was, in these severe and recurrent hospitalized patients, treatment was not seriously deficient. Compliance over the eighteen months was eighty percent of prescribed doses but about fifteen percent of the subjects declined to receive the prescription for an antidepressant. When we looked at the level of antidepressants used for continuation and maintenance, they were not ideal, but there were no major deficiencies, certainly not of the magnitude to explain high relapse rates, and at eighteen months, recurrence. The major problem the study revealed was the preference of patients, in some circumstances, not to take medication.

In an analysis of unmet treatment needs, we found failure to meet a medication need was, in the majority of cases, by patient refusal. When other needs for treatment were unmet, in the majority of cases they were by treatment-team inaction.

The issue of treatment acceptance is important. I had meanwhile become involved in the Defeat Depression Campaign in Britain. I was, for five years, chairman of its scientific committee and a member of the steering committee. This was a five-year campaign sponsored by the Royal College of Psychiatrists and the Royal College of General Practitioners, aimed at influencing public attitudes about recognition of depression and its treatment, as well as education of general practitioners about treatment. We undertook three general population surveys of attitudes; at baseline, at two and a half years and at five and a half years, after the end of the campaign. At baseline, the majority of patients regarded counseling for depression as effective.

TB: What percentage of patients regarded antidepressants as effective?

EP: Only forty percent felt antidepressants were effective and seventy eight percent regarded them as potentially addictive. That explains the kind of findings when patients refuse antidepressants. We did manage to influence attitudes toward antidepressants over the course of the five-year campaign and they became about seven percent more favorable by the end of the five years. That returns me to the theme of long term outcome because with those two studies we had been considering possibilities that might explain poor outcome

TB: Where did your support for research come from?

EP: Since the mid 1980s, virtually all my work has been funded by the Medical Research Council. We had a problem group of patients who had not responded well to medications but appeared to be receiving adequate medication and for whom it might not be the full answer. We all recognize these patients in clinical practice. Patients, who only show a partial response, often have side effects and changes of antidepressant, but the right one never seems to be available. There is a possibility we still have not got the right antidepressant for everyone, so we could do with more. We looked for a different form of treatment and the one that intrigued us was cognitive therapy. There were by now follow-ups from acute controlled trials which suggested that relapse rates were lower after cognitive therapy than after antidepressant treatment. But there are possible confounding factors. Perhaps the most important is the possibility that different kinds of patients are responding to cognitive therapy and antidepressants, and these groups may have different

spontaneous relapse rates. A second possibility is that in a number of studies drug continuation was not well controlled. So, we thought we had better do a controlled trial that was designed to look at relapse and recurrence and not at acute treatment. We undertook a controlled trial of cognitive therapy versus no cognitive therapy in patients with unipolar depression, who had suffered from a recent major depression which had partially remitted but showed residual Hamilton scores of eight or more and Beck Depression Inventory scores of nine or more. We wanted to ensure we were not primarily looking at undertreated patients pharmacologically, so we required all patients to be on an adequate dose of antidepressant. For the one third of patients on tricyclic antidepressants, this was a mean dose equivalent to one hundred and eighty-five mg. per day of amitriptyline. For the two third of patients on SSRI's, the mean dose was equivalent to thirty five milligrams daily of fluoxetine, and these dosages were maintained throughout a seventeen month study. Random assignment was to drug treatment and clinical management for half the sample, and to drug treatment and clinical management plus five months of cognitive therapy for the other half. This was a two-center study carried out in Cambridge and in Newcastle.

TB: Who were your collaborators?

EP: Professor Jan Scott, then in Newcastle, a psychiatrist expert in affective disorder and in cognitive therapy, and Dr. John Teasdale in Cambridge, a senior figure in the fields of cognitive therapy and mood-cognition relationships. The study commenced in the mid 1990's. The first paper on the findings was published in the *Archives of General Psychiatry* in September of this year, in 1999. Further papers are on the way.

TB: What did you find?

EP: A high relapse rate of forty nine percent over the seventeen months in the control group that was reduced to about twenty nine percent by cognitive therapy. All patients were taking adequate doses of medication; compliance was not affected by the cognitive therapy as it was good in both groups. Ratings were done by psychiatrists and independent raters, blind to cognitive therapy status, and we tried very hard to maintain that throughout the study. So, cognitive therapy did appear to be beneficial. Meanwhile, a small study had been published by Dr. Giovanni Fava in Bologna, using a similar, although not identical design, but a much smaller sample, which also appeared to show similar findings. We were pleased, but I don't view cognitive therapy as a substitute for antidepressants. Antidepressants are effective and do not require up to twenty

therapeutic sessions. If a psychological treatment is needed, it is in patients who don't respond well to an antidepressant. And, that was essentially the finding in this study. I find myself now, in a five center collaborative study of cognitive therapy in bipolar disorder, which will continue for some time to come.

TB: You have been involved in clinical research for almost 40 years. What would you consider your most important contribution?

EP: First, I think the life event studies. They were almost fortuitous and opportunistic, but they proved to be a very profitable vein, which has continued and gave me my first citation classic. My heart lies in the controlled trials of antidepressants and other treatments in depression. They include the Yale-Boston continuation study with amitriptyline and psychotherapy, which was a second citation classic, and also won the Foundations Fund Prize for Psychiatry from the APA, and the second prize from the Anna Monika Foundation. We are currently undertaking neuropsychological, PET scanning, and functional MRI studies in Cambridge, to look at brain neural mechanisms underlying depression; and that is a theme which is developing nicely. Dr. Barbara Sahakian, in the Department of Psychiatry, is my principal collaborator and the leader in these studies. They are expanding considerably, at the moment. But the life events work turned out well and the therapeutic trials may have done some good.

TB: Have you continued your epidemiological research in the aged?

EP: The research group goes on and is very active. It is a collaborative effort between psychiatry and epidemiology at Cambridge. We got involved in a second cohort of two thousand five hundred subjects, aged over sixty-five, from a different part of the Cambridge area, which is rural. This is part of a large-scale national study and is also linked to brain banking. I have progressively withdrawn from those studies, but I am still a member of the groups.

TB: You published many papers during the past decades. Could you say something about your first publication?

EP: My first publication was a letter to the editor of the *British Medical Journal* describing a patient who received a combination of methyldopa, an antihypertensive which is no longer used, and pargyline, that we now know to be a MAO B inhibitor. She had been treated by her general practitioner with both these drugs and had developed vivid visual hallucinations, apparently with clear consciousness.

TB: When was it published?

EP: In 1966.

TB: Could you say something about your last publication so far?

EP: Well, I now find it difficult to keep up, because what was the last publication last month is no longer the last publication this month. I suppose the last major publication was the cognitive therapy trial in September, but there have been about four more coming from our neuropsychological and other work. So, it goes on.

TB: You had a couple of citation classics. Any of your other work you think has had influence?

EP: The other work that has had influence was the continuation therapy study, and the work on general practice depression has had considerable influence, particularly in Britain, on the use of antidepressants in general practice. In the life events work, I am still asked to write reviews and our Interview for Recent Life Events is used widely by other groups. It is an area that we build into other studies. The naturalistic first follow-up study of depression in Cambridge also involved looking at life events, social support, marital relationships, expressed emotion, and their relationship to relapse. In that sample of severe and recurring depressives, life stress tends to fade into the background. Life events are of major importance in first episodes and perhaps second and third episodes, but with recurring episodes, depression becomes more autonomous.

TB: In addition to research, could you say something about your other activities?

EP: I am chairman of a department, which, although not large by American standards, is moderately sized by British standards and growing rapidly, so I have to look after that. That involves the usual mix of medical school and hospital activities, as well as building our research reputation; we are one of the best-rated departments in Britain for research, which is very important in the Cambridge environment. In the national research assessments of all university departments, which, takes place every few years, we have been in the very top group consistently. Then, there are other University activities. I am fortunate to be a member of the Syndicate of Cambridge University Press. The Syndicate oversees the activities of this very large university academic press. As a bookish man, being a member of the Syndicate has been a great pleasure to me.

TB: Am I correct that you were the founding editor of the Journal of Affective Disorders?

EP: I was, indeed. George Winokur and I founded it in 1979, and we got great pleasure in watching it succeed. Then I was asked if I would be prepared to become editor of Psychological Medicine,

a larger journal published by *Cambridge University Press*. The journal was founded and edited by Michael Shepherd and he was retiring. It is a major international journal across the broad spectrum of psychiatric research. Ultimately, I agreed to take it on and I have continued to be its editor from 1994 on, leaving the *Journal of Affective Disorders* at the same time.

TB: What about your clinical activities?

EP: In the hospital, I lead a small resistant affective disorders specialist unit, with a therapeutic team to help me. My personal clinical work is limited though, by lack of time.

TB: Any other university related activities?

EP: In the university, I am a Fellow of an ancient Cambridge College, Gonville and Caius College. Cambridge life is complex; we are all members or Fellows of a College, as well as of departments. I wasn't a Cambridge man, far from it, and I felt very fortunate to become a Fellow of this ancient college. Francis Crick, of the double helix, was a Fellow there, but has lived in the U.S.A. for many years. Sir Ronald Fisher, the father of modern statistics and analysis of variance, was a Fellow there many years ago. Stephen Hawking is a star, today.

TB: You have been a member of several professional organizations.

EP: I have been a long-time member of psychopharmacological organizations. I like joining things. As a young American researcher, I became a scientific associate of the ACNP in the late 1960's. After returning to the U.K., I ceased to be eligible, but I was fortunate to become a foreign corresponding member later. I first went to a CINP meeting, in 1970, in Prague, and that was a very seminal meeting, which certainly had an enormous effect on me. My wife was pregnant with our first American citizen child and also came. It was a sad time in Czechoslovakia after the ending of the liberalization of the Prague spring, with Soviet tanks outside the city. I have been a regular member and attendee of CINP congresses ever since, and suffer for my crimes by being president-elect, something I feel is a great privilege. I was an early member of the British Association for Psychopharmacology (BAP), its president many years ago, and now an honorary member. At one stage, I was very active in the Royal College of Psychiatrists and became its Vice President. I was also President of the Marce Society, the international association concerned with psychiatric disorders of childbearing.

TB: You have been very much involved in teaching and training.

EP: Yes!

TB: Would you like to mention some of the people you trained?

EP: I have been lucky, as I have had very talented younger collaborators. Of the people from my time at St. George's, several have now become professors, including Professor Cornelius Katona, who is a professor of the University College, London and Dean of the Royal College of Psychiatrists, Professor Thomas Barnes, an eminent psychopharmacologist in schizophrenia, Tony Hale, also a psychopharmacologist, and Ted Dinan, who was the professor at Barts and is now Professor of Psychiatry in the medical school at the Royal College of Surgeons in Dublin, Ireland. In Cambridge, David Healy, has emerged as a historian of psychopharmacology, like yourself, and is one of your collaborators. He is a young man with immense creativity. Now there is a group of younger people in Cambridge, who are traveling the same route.

TB: In addition to papers, you have also published a few books.

EP: I believe it would be eight books and I think now we are up to three hundred and four papers and chapters.

TB: Would you like to say something about your books?

EP: My first book was written with Myrna Weissman, out of our Yale work, and was called *The Depressed Woman*, published by *University of Chicago Press*. This was a study of the social relationships, measured by our Social Adjustment Scale, in a sample of depressed women from our therapeutic trial, and a sample of matched controls from the general population. My second book was a British Association for Psychopharmacology Monograph, edited with Alec Coppen, and called *Psychopharmacology of Affective Disorders*. It tells you where I stand. A major undertaking was the *Handbook of Affective Disorders*, first edition in 1982, and second edition in 1992.

TB: Was it translated?

EP: Well, the *Handbook* was translated into Spanish, and widely used in South America. All the time, I have had this balance between psychopharmacology and biological psychiatry, on the one hand, and social psychiatry, on the other. That's because I think they are both important and because I have enjoyed both. So, the most recent book, published a few years ago, was an attempt to look at the role of prevention in psychiatry. That again was an edited book, with Professor Rachel Jenkins, a British psychiatrist, now a professor at the Maudsley, who has been a very influential figure within the government department responsible for our psychiatric services, the

Department of Health. We tried to be cautious, but to be authoritative, and also point to a few future directions for prevention in psychiatry. We concluded that it would be unwise to invest large sums of money in psychiatric prevention, yet and that well-evaluated pilot projects were needed. In the long run, a mature branch of medicine has to have preventative techniques.

TB: Any new book coming?

EP: I have no new books coming, as books take a long time and currently my life is too busy to fit them in. I have been putting what little time and effort I have for publishing, into both editing a journal, and writing papers. TB: Do you have any private practice?

EP: No, in the British tradition, academics do not usually undertake private practice, although, that is slowly changing. But, as a man who works all hours of the day and night and is fortunate to have a family who have permitted that, I don't think it would be fair to anyone, including patients, to be seeing private patients.

TB: But, as I understood it, you are still seeing patients on your Unit.

EP: I also, every week, undertake a ward round on my inpatient unit, which is a detailed review of patients and deciding about their treatment, and every week I have an outpatient clinic, in which I see one patient, who invariably is a second opinion referral from another psychiatrist in Cambridge, or from further afield. This week it was a patient from New York with resistant affective disorder.

TB: You have given several prestigious lectures.

EP: I was the annual guest lecturer some years ago for the ACNP and, as you might guess, I spoke about antidepressants. I have been the annual guest lecturer for the BAP, talking about a similar theme. I have been the Maudsley Lecturer of the Royal College of Psychiatrists, which is the senior lecture of the Royal College. I was talking about the treatment of depression more broadly. And, this year, in March, I was the Gerald Klerman Memorial Lecturer at Cornell University Department of Psychiatry, describing our more recent work. Next year in April, I will be giving the first memorial lecture for someone who was a very dear friend and that's Brigitte Prusoff at Yale, who was the statistician whom I collaborated with for many years and one of the most helpful people I have had the privilege to know.

TB: Is there anyone else you would like to mention of people you collaborated with or who had a major impact on your career?

EP: I have mentioned a number of names over the course of this interview, such as Myrna Weissman. We were research siblings and collaborators and have been friends over many years. Of the senior figures who taught me and influenced me there were many. It's difficult to select people out, because, if one has any sense, one learns from everybody. It seems to me that, constantly throughout life, I had to learn new things because of demands my career and increasing age put on me. I have always done my best to learn from those around me, senior, contemporary, and younger. Nowadays, the young psychiatrists know so much more neurobiology than I ever learned. Much of it wasn't even known when I was a student.

TB: Is there anything we left out and you would like to add?

EP: On a personal side, yes. I grew up in a musical family. My mother kept active as a pianist throughout my childhood and adolescence in New Zealand. I learned the violin but I have a poor ear and gave it up. My two sisters are both musicians. One, living in England longer than I have been, was a flautist, a teacher of the flute and married to a professional violinist, so their life has been music. The other one, in New Zealand is a cello teacher. I love listening to music, but my service to music is not to perform it. My wife was a librarian at the Maudsley, when I met her. In later years, she has become a textile artist, very creative with a brilliant sense of color. Both she and I are very keen on music, theater, and opera. But we both have become so busy there is much less of that in our lives than there used to be. We have two adult sons, of whom we are proud.

TB: On this note we conclude the interview with Professor Paykel. Thank you, Gene for sharing this information with us.

EP: Thank you.

50. ALFRED PLETSCHER

TB: We are in Riehen, in the town of Basel, Switzerland. This will be an interview with Professor Alfred Pletscher⁵² for the Archives of the American College of Neuropsychopharmacology. It is January 25, 2002. I am Thomas Ban. Thank you very much Professor Pletscher for seeing us in your home. I would like to start from the very beginning. If you could tell us when and where you were born and brought up, as well as something about your early interests and mentors?

AP: Thank you very much, Professor Ban. I'm really honored that you and Mark came to see me and ask me some questions. I hope that I can answer them. I was born in the far east of Switzerland. It was about three miles off the eastern frontier, close to the river Rhine on the frontier with Austria. I also attended elementary school there. I did my studies in Zurich, Geneva, and Rome. I was in Rome for one semester, before the war, from 1938 to 1939. I decided to go there, because everybody went to Germany. We had a relatively flexible curriculum in our universities. We could move for a semester to other universities and many of us went for a semester to Berlin, Germany, or Vienna, Austria, or Rome, Italy. I studied medicine, graduated from medical school, and got my medical degree after I defended my thesis. Then, after practicing for a while, I studied organic chemistry, and again after defending a thesis I got my Ph.D. in organic chemistry.

TB: When did you graduate from medicine?

AP: I got my M.D. in 1942 and my Ph.D. in 1948.

TB: So, you are a medical doctor and an organic chemist.

AP: Yes. I was always inclined towards biology and I thought I would like to do medical biological studies and ought to get an education in chemistry. After completing my studies in organic chemistry, I returned to medicine and practiced for four or five years before I was approached by Hoffmann-La Roche and asked whether I would be interested to become their director of biological research.

TB: When was that?

⁵² Alfred Pletscher was born in Altstaetten, Switzerland in 1917. He received both his M.D. degree and his Ph.D. in organic chemistry from the University of Zurich, Switzerland. After a year as Visiting Scientist at the National Heart Institute of the National Institutes of Health, he returned to Switzerland to assume an executive position at Hoffmann - La Roche, Basel. After he left industry, he founded the Department of Research at the University of Basel. Pletscher died in 2006. He was interviewed in Riehen Basel, Switzerland on January 25, 2002.

AP: That was at the end of 1954.

TB: Could you elaborate on your early interests?

AP: I was interested in how biological processes work, and how to apply them. Also, I was interested in human relations and I had the idea that with sick people, you could get, perhaps, closer relations.

TB: Did you ever think of pursuing a different career?

AP: No. I wanted to help, to alleviate suffering. And, I liked medical studies, but after I got my degree, I had the impression I did not know enough, that I needed to do further studies. I thought of studying organic chemistry because most of our remedies come from biochemistry. I also believed we should not rush into surgery; if a leg is "sick" we should not cut it off. So, I became interested in how to prevent illness and the need to know biochemistry to understand biological processes. We were very much behind the United States at that time. The United States, in biology and biochemistry, was far advanced.

TB: We are talking about the early 1950's?

AP: Yes, after World War II. During the war, America made tremendous progress and we were lagging behind. I was rather idealistic, although you could ask, why did then I join the chemical industry, which is not so idealistic. I joined because I thought I would have more possibilities to help sick people than being a general practitioner. If I found a drug, and we found, for instance, Librium (chlordiazepoxide) and Valium (diazepam), we could then help thousands of people; as an individual physician, I could only help a few.

TB: You were frustrated about the state of art of treatment?

AP: Yes, but then I got a letter from Roche, who asked me to come. At first, I said no, and half a year later, they asked again. And Ciba also tried to get me, but I felt from my viewpoint, Roche was closer to my intentions than Ciba. It was a family owned company and the family created a very good spirit. The management of the commercial department would listen to what we, in research, said. And that is what I liked. Otherwise, I would not have joined them. Today, I would not join them anymore.

TB: I see. It was a family owned company.

AP: I knew the family very well. I knew the owner, Paul Sacher. He was, more or less, a friend of mine. His wife was a sculptor and he was a famous musician. He supported and created many,

many things. He has created a famous Archive of Stravinsky, which is in Basel. So, he was very much tied to culture, he had a cultured mind.

TB: Did Roche differ in any other respect from other major Swiss drug companies?

AP: It started as a pharmaceutical company; whereas, all the other ones, Ciba, Sandoz, Geigy developed from the dye industry and pharmaceuticals were not necessarily their priority, whereas Roche's priority were pharmaceuticals from the beginning. And, at Roche, research, from the very beginning, was important. They had several drugs at the time I joined them.

TB: Can you tell us about the drugs they had at the time?

AP: The biggest seller was a sulfa drug. It was a six million dollar business in the United States. Later we got to one billion dollar drugs. They had COX inhibitors and tonics. We had several good drugs marketwise that also made good profits, although I didn't care about those things.

TB: Were the companies that merged into Novartis, like Sandoz, Ciba, and Geigy, still separate at the time you joined Roche?

AP: They were. Ciba was probably the most famous one, but Roche had a good name.

TB: Didn't Ciba have reserpine at that time?

AP: Ciba had reserpine, an adrenergic blocking agent extracted from the root of Rauwolfia Serpentina, an Indian plant used as a tranquilizing drug in folk medicine in India. Ciba had extracted the active ingredient and introduced it in the treatment of hypertension because in animal pharmacological experiments, Bein found it lowered blood pressure. Then in the clinic, it was found also to have antipsychotic effects. They used it in schizophrenia and it was called a neuroleptic. At the same time, chlorpromazine came and these were the two neuroleptics available at the time.

TB: What did Sandoz have?

AP: Hydergine.

TB: Was Roche interested in developing CNS drugs?

AP: No. Roche had a CNS drug at the time that came out of serendipity. It was iproniazid, a monoamine oxidase inhibitor and the isopropyl derivative of isoniazid, one of the first successful remedies for tuberculosis. It produced euphoria in some patients that clinicians referred to as an antidepressant effect. It was Nathan Kline, with whom we had contact, who thought it was an antidepressant.

TB: Was isoniazid a Roche drug?

AP: No, isoniazid was not developed at Roche, but Roche had a patent for its use.

TB: What about iproniazid?

AP: Herbert Fox at Roche synthesized iproniazid, in 1951. They wanted to improve the therapeutic effect of isoniazid in tuberculosis.

TB: So, Roche had two effective drugs for tuberculosis.

AP: Yes. And it was a serendipitous finding that iproniazid had antidepressant effects because everybody at the time was looking for a better drug than isoniazid in tuberculosis.

TB: Iproniazid was synthesized just a few years before you joined Roche?

AP: A couple of years before. As a student, I had been a patient treated with iproniazid. That was in 1938, and before that there was no medication. All you had to do was lie down, be quiet, and eat well. Then you either died or survived.

TB: What you are saying reminds me of Thomas Mann's Magic Mountain. There was at the time no treatment for it.

AP: We just had to lie down and enjoy the mountain air.

TB: So, at the time you joined Roche, they had iproniazid.

AP: There were three drugs in those years, chlorpromazine, reserpine, and iproniazid with an effect on psychiatric patients. They didn't call them psychotropic drugs. Nothing was known about the mode of action, other than that iproniazid was a monoamine oxidase inhibitor. When I started, there were only three neurotransmitters known in the brain acetylcholine, serotonin, and norepinephrine. The presence of histamine in the brain was not demonstrated yet.

TB: Norepinephrine was just discovered in those years.

AP: Yes and Von Euler got the Nobel Prize for that. Nothing, or virtually nothing, was known about the transport, storage, and release of neurotransmitters, or about monoamine receptors in those years. There were hypothetical concepts about receptors but no solid physical evidence. All that came much later.

TB: So, this was the state of affairs when you joined Roche.

AP: So, when I joined Roche, I wanted to go to the United States for two reasons. One, they were much more advanced in biochemistry, and in order to do my job, I thought I would need to adopt what they had. The second reason was that our friends and associates at Nutley, in the US, told us

that exciting things were going on in Brodie's laboratory. I decided I would be interested to go there and do some research with him; Severinghaus asked Brodie for a letter of invitation for me, and I started in Brodie's laboratory, in March 1955. Brodie's closest collaborator, Parkhurst Shore, was a creative and intelligent young man. By the time I arrived, they had shown that both reserpine and serotonin, when injected into mice were sedating; they found that both perpetuated the hypnotic effect of hexobarbital. They also found the sedative effect of reserpine and serotonin was antagonized by LSD, lysergic acid diethylamide. Prior to their research, Gaddum reported that LSD, a potent hallucinogen, blocked the effect of serotonin on smooth muscle. Brodie and Shore had also shown that reserpine increased the excretion of 5hydroxyindole acetic acid (5-HIAA), the major metabolite of serotonin, formed by oxidative deamination via monoamine oxidase. They suggested that serotonin has a function in the brain and mediates the effect of reserpine. Not many people believed it. So, I decided I would try to find direct proof reserpine depletes serotonin. I was very meticulous in my research. Serotonin was known to occur in three places in the body; in the intestinal tract, the blood platelets, and the brain. By far, the highest amount of serotonin occurred in the gut, especially in the rabbit gut, so we thought the easiest thing, to begin with, would be using that. There was a colorimetric method I had to adapt before I could start with my experiments. After a couple of failures, when there was no color reaction, I found that reserpine releases and depletes serotonin. After we were certain, we published our findings in *Science*. Of course we had to show this also happens in the brain. Since the concentration of serotonin is much lower in the brain than in the gut, the colorimetric method I used was not suitable for these experiments. The problem was how to find a method with the necessary sensitivity that would make these experiments possible. Fortunately, in a laboratory close to ours at the NIH, there were two people working, Dr. Bowman and Dr. Sid Udenfriend, who had just created a new instrument, the spectrophotometer. With this instrument, the small quantities of serotonin metabolites showed up by activation of the fluorescent spectrum. Use of the new instrument made it possible for us to show that reserpine depletes serotonin in the brain. We could hypothesize that the psychotropic effect of reserpine was a biological effect mediated by an endogenous neurotransmitter.

TB: Wasn't there a correlation between reserpine induced sedation and serotonin levels in the brain?

AP: Yes, it was a correlation between sedation and serotonin levels. It was a crucial experiment.

TB: And, the findings were published?

AP: They were published, in 1955, in *Science*.

TB: It was this discovery that opened up the field of neuropsychopharmacology.

AP: Absolutely. It was interesting to see that a psychotropic drug affected an endogenous neurotransmitter.

TB: It has profoundly affected the development of neuroscience. Just a couple of years before these findings were published, people argued whether neuronal transmission was predominantly electrical or chemical.

AP: The evidence for chemical transmission grew during the 1950s and interest became focused on monoamines involved in neuronal transmission. There was also another psychotropic drug in those years, iproniazid from Roche in Nutley. Reserpine was tranquilizing and was known, in certain cases, to cause mental depression, whereas iproniazid had the opposite effect on mood and behavior. So, I did an experiment on its effect on serotonin in the brain and found that iproniazid antagonized the reserpine induced decrease of serotonin. Reserpine, alone, might have decreased serotonin but pre-treatment with iproniazid prevented both the decrease of serotonin and the concomitant behavioral changes.

TB: You also showed that reserpine decreased, whereas iproniazid increased, serotonin.

AP: When I told Professor Kline that reserpine and iproniazid have the opposite effect on mood and serotonin levels, he was enthusiastic about my findings and said, "Now I believe we have something."

TB: When you decided to go to work with Brodie, did you have in mind that you would do research with iproniazid?

AP: No, I went there to become acquainted with American research in biochemistry. I was always interested in brain research, and I heard there was interesting research going on in his laboratory. While working there, I became one of the main actors who found reserpine has a direct effect on serotonin in the brain.

TB: It was your task to show that reserpine depletes serotonin, not only in the gut, but also in the brain?

AP: I provided direct proof that reserpine depleted serotonin in the hypothalamus.

TB: In addition to Parkhurst Shore and Steve Brodie, was there anyone else you collaborated at NIH?

AP: I was working mainly with Park Shore, and, of course, Brodie. We had a tremendous, stimulating environment. We had people around us like Sidney Udenfriend, like Julie Axelrod, and I learned a lot from them. And, when I came to the end of my stay, Arvid Carlsson arrived, and I got to know him. When I returned to Roche, in Basel, at the end of the year, as Director of Biological Research, I had the necessary authority to make the development of psychotropic drugs central in our program. I said that we should look for new psychotropic drugs with all the knowledge we have. We assembled a group of people for that research, found, and developed several compounds.

TB: Could you tell us about some of the drugs you developed at Roche?

AP: I wanted to find and develop a reserpine-like substance that would deplete serotonin in the brain. We were lucky to find the benzoquinolizines, a group of drugs that depletes serotonin and produces sedation in animals. In the clinic, they had been shown to have a neuroleptic effect, but they could not compete with chlorpromazine. It led to my second paper in *Science*, on the release of hydroxytryptamine by benzoquinolizine derivatives with sedative actions.

TB: And, this was in?

AP: 1957. It confirmed that certain psychotropic drugs were acting on endogenous substances like serotonin in the brain.

TB: The recognition that some psychotropic drugs act on endogenous neurotransmitter substances was a breakthrough, in itself.

AP: But it was only slowly that the medical community accepted that.

TB: In your recollection, who were the ones who recognized it first?

AP: Nate Kline, really; he was the person who recognized it.

TB: What about Joel Elkes?

AP: Elkes was one of them, yes.

TB: So, after you returned to Basel, you were trying to develop reserpine-like neuroleptics. Were you also interested in developing iproniazid-like antidepressants?

AP: I was always interested in antidepressants. We started a whole program on monoamine oxidase inhibitors. Some of the drugs that came out of that program probably are still in use. By

that time, other drug companies became interested in psychotropic drugs and were anxious to see what we did.

TB: It seems that pharmacologists and the pharmaceutical industry recognized much faster the new perspective opened by psychotropic drugs. Wasn't Fridolin Sulser asking your advice in the late 1950s, where he could get experience in the new field? I suppose you knew each other?

AP: I knew him only when he came to my office and said, Dr. Pletscher, I want to go to America. Where should I go? And I said, you would get a great experience in Brodie's laboratory if you are interested in neuropharmacology. That is the place to go to learn about the biochemical action of new drugs.

TB: So, it was you who suggested Fridolin go to work with Brodie. While working at Roche, weren't you also involved in teaching at the University?

AP: I always had a connection with the University. I taught pathophysiology in the medical faculty and I was a professor there. But one day the Chairman of Roche told me we were creating a new institute for clinical research in Nutley, New Jersey and they would like me to go there and reorganize research.

TB: When was that?

AP: I think, in 1957. So I went there and my wife came with me. It was not an easy time. I had to reorganize the whole thing. Nothing was being developed at the time I arrived. When I said, let's look at what we have, I was told there was nothing. Actually, they had a substance with the code name Ro 5-0690 (chlordiazepoxide), but management was not interested in it.

TB: Was Ro5-0690 the code name of one of Leo Sternbach's benzodiazepines? Wasn't he with Roche in Nutley at the time?

AP: Sternbach was at Nutley with us. After he left Poland, he worked in Switzerland, first, as an assistant at the Swiss Federal Institute of Technology in Zurich; then, he joined Roche in Basel. Prior to the outbreak of World War II, he moved to the United States and some years later he became Director of Medicinal Chemistry of Roche's research facility in Nutley.

TB: Did you know him well?

AP: Yes, he's a friend of mine. He synthesized this chemical substance and nobody knew how it worked biologically. It had a different structure from other drugs. So, I thought we should try it. Why not?

TB: The story one usually hears is that the substance was on the shelf, found during a laboratory clean up, and submitted for pharmacological screening because of the interest of the company in developing chlorpromazine or meprobamate-like psychotropics, which were a phenomenal success in those years.

AP: The management at Nutley was not interested in developing a psychotropic, but regardless, the substance was sent for pharmacological screening. Then, one day, Lowell Randall, our director of pharmacological research, asked me to come to his office. He told me he had a couple of wild, untamed aggressive cats, and about twenty minutes after he gave them Ro5-0690, they became pussycats. But the main thing was the cats were not sleepy. They were tranquilized without losing coordination.

TB: Am I correct that behavioral changes with Ro5-0690 were similar to what Frank Berger saw with meprobamate?

AP: Yes, the only difference was that we saw it in cats.

TB: I wonder whether Randall would have picked it up, even without knowing about the pharmacology of meprobamate. But, undoubtedly he was familiar with it. Did you know Frank Berger?

AP: I met him just one or two times, but we did not discuss much about pharmacology. He was successful with his drug. I was responsible for the whole research program that developed Librium. Sternbach, of course, was the one who synthesized the drug, and Randall did the pharmacology.

TB: If I understood you correctly, the management did not want it.

AP: Mr. Hoche, the sales manager told me that there was no market for these drugs.

TB: But fortunately, you succeeded in moving ahead with the substance. Do you remember who, were the first people on the clinical side working with the drug?

AP: No, I don't.

TB: Was it Joe Tobin?

AP: It was not Tobin, he came later.

TB: Librium promptly became a great commercial success.

AP: By that time, I had returned to Basel.

TB: When did you return to Basel?

AP: That was in 1958, or so.

TB: So, all the research that led to the release of Librium, one of the first blockbuster drugs, was done, in 1957 and 1958. If I remember well, the first publications appeared, in 1959 or 1960.

AP: Yes. It was amazing.

TB: It moved very fast. And Librium was soon followed by diazepam, Valium.

AP: Once we had the experience with Librium, we found developing Valium much easier.

TB: What was the purpose of developing another benzodiazepine with a similar pharmacological profile to Librium?

AP: We wanted to have a benzodiazepine that was more potent than Librium. But there are not only scientific, but also commercial, considerations in drug companies for developing compounds.

TB: After your return to Basel from Nutley, you were appointed Director of Research of Roche International.

AP: Yes.

TB: Could you tell us about your activities in the new position?

AP: I had to organize a more or less new department. We continued our work with the benzoquinolizines and one of the substances, tetrabenazine, we thought to develop into a short acting neuroleptic. It was submitted for clinical trials and showed neuroleptic type activity but it could not compete with the neuroleptics already in clinical use.

TB: What about benzodiazepines?

AP: We did further research with Librium, and developed several benzodiazepine derivatives, not only for the treatment of anxiety disorders, but also for insomnia and the control of seizures in epileptics.

TB: You also had the thioxanthene analogue, chlorprothixene.

AP: Yes, chlorprothixene was our drug. There were two companies that developed it. In fact, we also had amitriptyline.

TB: So you were involved in developing anxiolytics, antipsychotics, and antidepressants.

AP: We also had antibacterial agents as part of our profile. It was an important line of research at Roche, even if psychotropics were at the center of interest at the time.

TB: I distracted you by asking you about chlorprothixene.

AP: We wanted to know everything about the mechanism of action of the benzodiazepines. Some of this work was focused on their action on the inhibitory neurotransmitter, γ -aminobutyric acid.

They have an agonistic action on post-synaptic GABA-ergic mechanisms. As you know, specific benzodiazepine receptors, binding sites, have been characterized in several vertebrate species.

TB: I suppose your group collaborated with outside researchers?

AP: We collaborated with Erminio Costa at NIH and with researchers in the department of pharmacology at the University of Basel. And we also collaborated with many other researchers.

TB: You already told us the background to the development of benzoquinolizines, benzodiazepines, and iproniazid, but how did you get to developing chlorprothixene?

AP: We had a battery of tests to screen drugs for their possible psychotropic effects and our screen indicated the substance might have neuroleptic effects.

TB: Was it a behavioral pharmacology screen?

AP: Behavioral pharmacology; there was no biochemical pharmacology screen at the time.

TB: Was the drug synthesized at Roche?

AP: It was. We got to it by molecular manipulation. We had the patent.

TB: What about amitriptyline. Did you get to it also by molecular manipulation and behavioral screening?

AP: Yes.

TB: In the development of benzodiazepines, Leo Sternbach and Lovell Randall played an important role. Is Sternbach still alive?

AP: Yes, he's 94 years old, but he still goes to the office every day; his wife takes him to his old office.

TB: Where is his office?

AP: In Nutley. He lives in Montclair, New Jersey.

TB: What about Randall?

AP: I lost sight of him. He moved to California. It was Randall who discovered that Ro5-0690 might be an anti-anxiety drug. You could say it was a serendipitous discovery.

TB: Chlordiazepoxide was an immediate success in North America.

AP: Yes.

TB: What about in Europe?

AP: Also. The nurses were stealing it from the hospital pharmacies, in order to try it on their patients. One of our managers told me, if the nurses steal, we must have a successful drug on the market.

TB: Is there any other drug related to neuropsychiatry you were involved with we should talk about?

AP: Are you interested in benserazide?

TB: Yes, of course.

AP: It is an extracerebral inhibitor of decarboxylase that enhances the effectiveness of levodopa in the treatment of Parkinson's disease.

TB: How did you get to it?

AP: It is a long story.

TB: Tell us.

AP: It starts with Arvid Carlsson's discovery that dopamine is a neurotransmitter and not just a mere intermediate in the synthesis of noradrenaline and adrenaline, and Sidney Udenfriend's recognition that DOPA is the biological precursor of dopamine. Dopamine is the decarboxylation product of DOPA.

TB: Wasn't Udenfriend with Roche at Nutley?

AP: Yes, he was. The discovery that dopamine occurs in relatively high concentrations in the brain centers responsible for the control of extrapyramidal movements, and Carlsson's findings that DOPA antagonized the reserpine-induced motor depression and decrease of cerebral dopamine, led to the assumption that dopamine was involved in the regulation of extrapyramidal motor activity. This is the background to Ehringer and Hornykiewicz's findings, in Vienna, that the concentration of dopamine in the striatum of deceased patients with Parkinson's disease is lower than in controls.

TB: Weren't some findings indicating decreased dopamine in Parkinson's disease reported from Montreal about the same time?

AP: I think it was a little bit later that Barbeau, Sourkes, and Murphy, in Montreal reported that in patients with Parkinson's disease, the urinary excretion of dopamine was markedly decreased, indicating also a dopamine deficiency.

TB: I see.

AP: Since dopamine does not cross the blood brain barrier, whereas L-DOPA does, these findings led to trying L-DOPA in patients with Parkinson's disease by Birkmayer, in Vienna and Barbeau, in Montreal.

TB: I remember meeting Barbeau about that time. He passed away a few years later. Both papers were published in the same year.

AP: It was, in 1961. Birkmayer's paper was coauthored by Hornykiewicz and Barbeau's by Sourkes and Murphy. In both papers, symptomatic improvement was reported with levodopa in Parkinson's disease. Our contribution to the treatment was adding benserazide to the regimen. The idea was to improve the effectiveness of treatment by protecting the amino acid from further metabolism and inactivation in extracerebral tissues.

TB: Was benserazide introduced as a combination with levodopa?

AP: Not by Roche, but by Pfizer about the same time, in the 1960s.

TB: Weren't monoamine oxidase inhibitors also tried by Birkmayer to decrease the dose requirement of levodopa?

AP: You mean levodopa, together with a decarboxylase inhibitor and a monoamine oxidase inhibitor?

TB: Yes.

AP: At the time, there was no monoamine oxidase B inhibitor available and combining levodopa with a non-selective monoamine oxidase inhibitor caused too many side effects.

TB: When did you step down from your position at Roche?

AP: I was Director of Research Worldwide from 1967 to 1978.

TB: What did you do after you stepped down?

AP: I was asked to create a Department of Clinical Research at the University Hospital in Basel, and I did that. The department still exists and it's doing very well. The clinical research building is in the middle of the hospital complex.

TB: So you moved from Roche to the University.

AP: As I told you, I always taught at the University, even while I was with Roche.

TB: Could you tell us about your activities in the Department of Clinical Research at the University?

AP: I created first a group that worked in hypertension, then a group that worked in oncology, and a group dedicated to brain chemistry, and also some other groups. I was Director of the Institute, but I had a research field of my own.

TB: What was that?

AP: It was my idea of using platelets as a model for the brain, and I was studying in platelets the mechanism of monoamine uptake, storage, etc. Many people still use platelets to screen for monoamine uptake inhibiting drugs. It is especially suitable for studying serotonin uptake, which is different from norepinephrine uptake. For the study of norepinephrine uptake, the model is not as good. We discovered that serotonin is stored in organelles and showed that reserpine releases serotonin from these organelles. The biochemical work was mainly done with my Italian friends.

TB: When did you start to work with the platelet model?

AP: I started in the early 1960's.

TB: Any other research you would like to talk about?

AP: We did research in hypertension with β -blockers, and research in immunology related to organ transplants.

TB: For how long were you director of the Institute at the University?

AP: For almost 10 years. I retired from my chair, in 1988, and became President of the Swiss Academy of Medical Sciences. Prior to that, while I was still with the University, I was President of the National Science Foundation. I was also the President from 1981 to 1987 of the Research Council and the Administrative Council of the National Science Foundation.

TB: Have you kept contact with Roche after you left the Company?

AP: Yes, I was a consultant for many years. I went to their CNS meetings and remained involved with their clinical research. My successor was a pupil of mine.

TB: Roche continued the research you started with monoamine oxidase inhibitors?

AP: Although Zeller was my appointment, he discovered iproniazid's monoamine oxidase inhibiting effect before I joined the company. He was working at a University in Chicago, at the time, when he discovered that iproniazid inhibits monoamine oxidase. He had been involved with monoamine oxidase since the late 1930s. But we did, later on, develop inhibitors of both monoamine oxidase A and monoamine oxidase B enzymes at Roche. I don't know whether we would have entered this area of research if we had not discovered that iproniazid is an

antidepressant and without my findings that iproniazid and reserpine had the opposite effect on mood and serotonin levels in the brain. The company ultimately developed a monoamine oxidase A inhibitor for clinical use. Have you heard of it?

TB: I'm familiar with moclobemide. I think it was introduced in the early 1990s. What happened with the monoamine oxidase B inhibitor line?

AP: The company was not interested in it.

TB: During the past 50 years, you had numerous publications.

AP: I published first when I was still at the University, and my last paper on the winding path of the history of antidepressants was published, last December.

TB: 2001?

AP: Yes. I also reviewed the history of anti-Parkinson drugs. But these last publications are reviews and not reports on our original work.

TB: During your distinguished career, you received many honors and awards. Could you mention a few?

AP: The first one I got was a Science prize. Then, I got the Marcel Benoist Prize. It is the highest prize in this country, given to Swiss scientists. I was elected honorary doctor and received honors from the University of Basel, Geneva, Rome, Zurich, and several other universities.

TB: You recognized early that progress in treating disease depends on the development of drugs.

AP: This was why I joined the industry; although, I did not necessarily agree with everything industry is doing.

TB: What is your problem with industry?

AP: It's too commercial. All the decisions are made by non-scientists with the involvement of lawyers, commercial people, economists, and the like. All of us are trying to make a contribution to society and making money should not be the primary objective. Of course, you need money. You have to earn money. That's clear. Without money there's no research. My primary motivation was not profit but helping people.

TB: You are very idealistic.

AP: But I also have to add I got a good salary at Roche, and I'm thankful for that.

TB: You contributed to helping patients with your new drugs.

AP: It was satisfying I could make a contribution in that way. As I said before, as a practitioner, I would have been able to help only a small number of patients.

TB: What would you consider your most important contributions to neuropsychopharmacology?

AP: I would say our contribution to the treatment of Parkinson's disease; introducing the use of platelets as a model of the brain for studying uptake, storage, and other processes in the neuron, and of course, our demonstration that the effect of some psychotropic drugs is mediated by endogenous neurotransmitters.

AP: You have also contributed by training many people. Is there anything else you would like to mention?

AP: Oh, my family. I have a very happy family. My wife is from Zurich. I think she deserves an award, because I was away from home very often. I am also proud of my children. I have a daughter who is a physiotherapist and a son who is a medical doctor. They helped me out often. I don't know whether I helped them. I also have five grandchildren.

TB: I heard from somebody that you are a sportsman.

AP: I'm a hiker; I did a little bit of mountain climbing and skiing. I also did marathon runs; I did it several times and I'm proud of that.

TB: What are you doing these days?

AP: There are many things I don't do any longer, but I try to keep up with what's happening in genetics, in molecular engineering, and in the ethical dimension. I think you have an obligation to work for yourself, but you also have an obligation to contribute to your fellowmen. That's it.

TB: On this note, we should conclude this interview with Professor Alfred Pletscher. Thank you very much for sharing this information with us.

AP: Thank you.

51. ROBERT M. POST

TB: This is the annual meeting of the American College of Neuropsychopharmacology. We are in Hawaii. It is December 9, 2001, and this will be an interview with Dr. Robert Post⁵³ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Where and when were you born? Tell us something about your early interests, education, and how you got into neuropsychopharmacology.

RP: I was born September 16, 1942, in New Haven, Connecticut. I always had an interest in psychology and when I was an undergraduate at Yale, Robert Galambos gave us lectures on REM sleep. He told us about all the amazing neural activity that was happening and it turned me on to the whole issue of brain activity and behavior.

TB: So, Robert Galambos's lecture had a major impact on you. Did you have any contact with him later?

RP: Not really. Even before I listened to Galambos' lectures my interest was tweaked about the brain by being a nurse's aide on the Yale inpatient psychiatry unit.

TB: You were born in New Haven and were an undergraduate at Yale?

RP: Yes. I wanted to go to school any place in the country except Yale, but my internist encouraged me to apply and I got in. I didn't bother applying to other places, so that's how I ended up there. I was a psychology major and that continued to stimulate my interest. Galambos came by for these lectures and, all of a sudden, I realized that everybody knew how the heart and the kidney worked, but the brain was a virtual mystery. Anything you found out about it, like REM sleep, was going to be new. That's how I got intrigued by neuroscience.

TB: When did you decide to become a physician?

RP: When I was young, a kid with cerebral palsy knocked on the door of our house, and I was shocked and distressed looking at him. Based on the image of that person and his suffering, I wanted to help people in some way, as a physician.

⁵³ Robert M. Post was born in New Haven, Connecticut in 1942. He received M.D. from the University of Pennsylvania. His clinical training began at Albert Einstein College of Medicine in New York City, New York, continued at the Massachusetts General Hospital in Boston, Massachusetts and was completed at the Intramural Research Program at the National Institute of Mental Health in Bethesda, Maryland. He was interviewed in Waikoloa Village, Hawaii on December 9, 2001.

TB: Where did you go to medical school?

RP: At the University of Pennsylvania and then I had I mixed medical, neurology, and pediatrics internship at Einstein in the Bronx.

TB: Where did you do your residency?

RP: I had one year of psychiatry residency at Mass General Hospital, when Biff Bunney, at the NIH, called and said, "We just had a researcher drop out. If you want to come as a clinical associate to the NIMH, we have a slot for you. If you come after three years, as a full psychiatric resident, we may or may not be able to take you in." So, I went to the NIMH. Biff Bunney, Fred Goodwin, and Dennis Murphy, interviewed me and they asked, "What do you want to do?" I said, "I don't know, I'll do anything you want." They weren't very impressed, so I think they drew straws for who would not have to work with me, and Fred Goodwin lost, so he got me.

TB: How did Biff Bunney know about you?

RP: I'd applied to NIMH several years before but I didn't pass the FBI background check for some unknown reason. I still don't know why they said I was not eligible to enter the Public Health Service, but I remember saying when I was told I was not eligible, "You mean, I can be sent to Vietnam but I'm not good enough for the Public Health Service?" They said, "Yes," I said, "Why?" And they said, "We can't tell you." I had my brother-in-law, a lawyer, who was in the Civil Liberties Union, start talking to people, but he could never find out what was wrong. However, he stirred up enough Senators and Congressmen to confirm there wasn't anything bad enough to disallow me from being in the Public Health Service. So, finally, I did get to the NIMH, but that was a very anxious year for me. They thought I had done some terrible thing, but I had no idea what that might be.

TB: Anyway, you got the job.

RP: I finally got in.

TB: What year did you get to NIH?

RP: In 1970, and I've been there more than thirty-seven years. Early in that clinical associateship, since I didn't know in which research direction I should go, Biff and Fred said, "Why don't you study cocaine? It's a potent facilitator of the catecholamines and induces euphoria; it should be a good antidepressant." I thought it was a silly idea, giving cocaine to depressed patients, but I said, "OK, if that's what you want me to do." The same thing happened in medical school. Dr. Jerry

Smith, in physiology, was assigning topics and said, “You, Bob, should write about the role of the amygdala in the regulation of eating and affect.” I said, “You really want me to write on the amygdala?” I thought that was a really silly idea, too. But from that time forward, the amygdala has been involved in almost all of my thinking about affective illness, as well as in bipolar disorder. These assigned topics turned out to be very big influences in the direction of my career. I didn’t choose those two topics, they were given to me, and I took off and ran with them.

TB: Did you ever resume formal training in psychiatry?

RP: I got one year of residency credit for the two years at NIMH and I needed another year to finish. I went to George Washington Hospital, and took seminars, particularly in child psychiatry. After two years working with Arnold Meyersburg, I got another year of credit. That was at a time when they could approve three years at three separate places. They don’t allow that any more.

TB: Were you involved in seeing patients and clinical work all through the years at NIMH?

RP: Yes. The first year, when I was a clinical associate, I worked with Joel Kotin, who has gone on to do psychoanalysis in Southern California. He was the ward chief and I was the person who was responsible for screening patients. Dr. Kotin was very skilful with those very difficult patients and extremely helpful in terms of getting my clinical career off the ground. I was very anxious about how to manage severely ill patients in the complexity of a clinical research environment. It was quite an education. Between Kotin’s friendship and support and Fred Goodwin’s mentoring, my research took off in the area of bipolar illness.

TB: Could we get back to your research with cocaine in depression?

RB: It turned out cocaine was not a very good antidepressant in serious depression. However, I got very interested in the acute and long term effects of cocaine, and found it paradoxically produced behavioral sensitization, rather than tolerance. Animals showed increased amounts of activity and stereotypy on repeated treatment and rats started having seizures on the same dose of cocaine, which they previously tolerated well. So, what I observed was kindling-like phenomena.

TB: You observed kindling-like phenomena with cocaine?

RP: Graham Goddard had just discovered, in 1969, electrical kindling of the amygdala. There was evidence that cocaine and lidocaine, as local anesthetics, were activating the amygdala and I began to think these drugs were kindling seizures, just like Goddard was with electrical stimulation. I began to study acute and chronic cocaine administration in animals to figure out

why there was increasing response to cocaine over time, in terms of behavior and seizures, rather than tolerance. That study of kindling focused me on the amygdala and subsequently to the anticonvulsants, such as carbamazepine, which are particularly good in inhibiting amygdala kindled seizures.

TB: When was that?

RP: In the early 1970's, we got interested in that with Jim Ballenger, and postulated that if we could quiet the excitability of the amygdala, maybe we'd get mood-stabilizing effects. Also, patients with temporal lobe epilepsy were having positive effects on mood with less depression when given carbamazepine (Tegretol). Based on these empirical data and the kindling notion, we became involved in research with carbamazepine. Just as we were getting started, we found out Okuma in Japan had positive data on the mood stabilizing effect of carbamazepine in open studies. From the second patient in our double-blind study, we learned that carbamazepine was an effective antimanic agent, because he got substantially better on the active drug, relapsed when it was substituted with placebo, and responded again to the active drug. This was somebody who, at baseline, was very psychotic; he was hallucinating, screaming, and had to be kept in seclusion. He was non-responsive to lithium yet was a really good responder to carbamazepine. From this off-on-off-on trial, we knew it would work for some people, and the only question was on what percent of patients. Currently, there are nineteen controlled studies showing that carbamazepine is effective in acute manic patients and more than a dozen that it is effective in prophylaxis.

TB: So, you were familiar with the Okuma's work in Japan when you started your carbamazepine studies.

RP: We found out about the Japanese work as we were thinking about using carbamazepine as a way of quieting down the amygdala system. We were already onto that idea, when we found out they already had preliminary open data before our controlled studies.

TB: But you did the first double blind study using the on-off-on design with carbamazepine?

RP: Yes. In the mid 1970's, we did the first controlled study and published it in 1978. Shortly after, in 1979, Okuma published a controlled study and a lot of other groups followed suit.

TB: Were you looking for an alternative treatment to lithium?

RP: Yes, and it turned out to be very productive territory; now, other anticonvulsants are looking very good in the treatment of bipolar illness, particularly the latest, lamotrigine. Lamotrigine looks

like it has excellent antidepressant effects, as opposed to carbamazepine and valproate, which have better antimanic than antidepressant effects. Lamotrigine has a different clinical profile and it may become a very important drug for bipolar depressed patients. In bipolar illness, depression is the most difficult component to treat.

TB: What response rate did you get with carbamazepine in your studies?

RP: About a sixty percent response rate in acute mania in people who failed lithium, so carbamazepine worked in some of the patients we were most interested in treating. Patients, who did not respond to what was conventional treatment in the community, came to us at the NIMH to participate in our research studies. So, a fifty to sixty percent response rate was pretty good in this treatment refractory subgroup of the bipolar population.

TB: That is a pretty good response rate in this population.

RP: Yes, and all our studies were double-blind with placebo control, using the off-on-off-on design, and in many responders, another round of placebo followed the carbamazepine to confirm individual responsiveness on a double-blind basis.

TB: Did you work with any of the other antidepressants or anticonvulsants in bipolar patients?

RP: I worked with lamotrigine and gabapentin. In a placebo-controlled parallel group study, it turned out lamotrigine was significantly more effective than either gabapentin or placebo in bipolar illness and in depression.

TB: Didn't you work, at a certain point in time, with Irwin Kopin?

RP: After I was at the NIMH, as a clinical associate for two years, I had the opportunity of going either to Yale, to work with George Heninger and Malcolm Bowers, or to Pittsburgh, to work with David Kupfer, or staying at the NIMH. After much agonizing, I decided to stay at the NIMH and had a third year fellowship with Irv Kopin, during which I did some work in the lab.

TB: What did you do with Irv?

RP: I worked on catecholamine metabolism and the effects of stress, but I didn't become a lab person like most people did. I continued my clinical research work but was very influenced by Irv's work on catecholamines and stress.

TB: Is there anyone else you worked with?

RP: Jerry Smith, the physiologist, back in medical school who tweaked me into studying the limbic system.

TB: With whom did you work after Irv?

RP: After the year with Irv, Biff Bunney offered me a job in his Biological Psychiatry Branch, and I took over running a clinical research unit. On that unit, I was greatly influenced by all of the young clinical associates who came to work with me. John Carman and Fred Stoddard were the first. Carman had what appeared to be the ridiculous idea that calcium was important in signal transduction and we studied plasma and CSF calcium, which nobody else did. Now it turns out that calcium is a central player in signal transduction. Carman also had the idea that dopamine was important in depression. At that time, everybody else was thinking about norepinephrine and serotonin in depression. There was Schildkraut's catecholamine hypothesis, Bunney and Davis had norepinephrine as the key substance in their theories of mania and depression, and Curzon, Van Praag, and others had serotonin as a central player. Then, here's this young kid, Carman, with a big beard and high heel shoes, saying that "dopamine is the critical player." His ideas directed us towards the role of dopamine in depression and mania, another theme I never really left. With Bob Gerner and David Jimerson, we studied a direct dopamine agonist used for Parkinson's disease, called ET495 or piribedil, which turned out had very nice antidepressant effects. This work helped bring the role of dopamine in affective illness into the foreground. Then, dopamine re-uptake blockers came along as antidepressants.

TB: When did you begin with this line of research?

RP: That began about four years after I arrived. During my first year as head of a unit, I was studying bipolar illness. The first two patients were profoundly manic; they left the unit and threatened the President of the U.S. and the head of the NIH. They were running all around before we figured out how to contain them. It was very interesting to learn how to approach and treat patients with bipolar illness.

TB: Didn't you also work with unipolar patients?

RP: I did some work with refractory unipolar depression, but for the last twenty-five years I always had about two-thirds, bipolar patients and one-third, refractory depression patients on our research unit.

TB: You said Carman generated some research projects with calcium and also with dopamine. Did any of the other clinical associate generated new projects?

RP: Each clinical associate who came to work with me brought some novel ideas. We tried to run with those as much as possible and that turned out to be very, very productive. We got into research with thyrotropin releasing hormone (TRH) with other associates. One of the latest associates was Mark George, who started work on our unit using repeated transcranial magnetic stimulation (rTMS) of the brain, with Eric Wasserman and Mark Hallett of the Neurology Institute. We're the first group to use high frequency, 20 Hz, repeated stimulation of the brain with magnets, over the left prefrontal cortex in depression. Now rTMS is looking promising as an antidepressant modality. We're currently comparing the effect of high frequency 20 Hz, and low frequency 1 Hz rTMS with Andy Speer on cerebral blood flow, as measured by PET, and we found that 20 Hz produced a long-lasting, widespread increase in blood flow, while 1 Hz decreased it. Individual patients appear to respond preferentially to high or low frequency rTMS, and we are trying to see if we can predict this on the basis of their pre-treatment PET.

TB: So, you got involved after your arrival at NIMH in areas of research you had little or no prior experience with, as well as using sophisticated technology.

RP: That was clearly the case. When I arrived at NIMH, learning neurochemistry was like learning a foreign language. I had no idea what the catecholamines were or what the term biosynthetic pathway meant. They were talking rapidly in this foreign language and I didn't know any of the words. I was a complete foreigner but became totally immersed in the atmosphere.

TB: You had to learn that new language fast.

RP: I tried.

TB: You had to feel as if dropped into another country.

RP: You had to learn quickly if you didn't want to starve to death.

TB: But you got involved promptly with bipolar patients?

RP: Yes, I was taking care of bipolar patients, who we had to get better even though lots of them were not responding to lithium. That drove us to look for alternatives and that's how we got to study the anticonvulsant, carbamazepine. It was to quiet down the limbic hyperexcitability, the affective dysregulation, that Papez, MacLean, and others postulated.

TB: Where did you get your patients from?

RP: They were referred from all over the country and sometimes from outside the US. That's continued to this day, but patients are now even more treatment refractory than they were in early

days. They used to come in just non-responsive to lithium. Later, they were non-responsive to lithium and carbamazepine, and so, we had to try valproate. More recently, they are coming non-responsive to lithium, carbamazepine, and valproate, so we have started a new protocol with lamotrigine. Lamotrigine worked about 50% of the time in these highly treatment refractory patients and was superior to both gabapentin and placebo. We have been getting more and more refractory patients over time. In the seventies, we used to be able to discharge patients on one drug, and we could do that about seventy-five to eighty percent of the time. We had good success early on, sending them back on one drug. Now we achieve the same positive results, but it takes three or four drugs on average. So it's getting harder and harder to stabilize these patients.

TB: How much neuroleptics, are you using?

RP: At NIMH, we had this unique opportunity to try to find treatments without the usual time limits. Since patients then could stay as long as they need, it was possible to use the time to try and figure out what would work, even if the first several drugs we tried didn't help. We were able to explore different treatment strategies, and, as a result, discharged almost all our patients without the need for neuroleptic treatment. Only about ten to fifteen percent of the patients had neuroleptics in their regimen when they left the NIMH. We could deal effectively with manic psychosis and psychotic depression without neuroleptics, which was important in terms of trying to avoid tardive dyskinesia. We were working largely with lithium, mood stabilizing anticonvulsants, thyroid augmentation and nimodipine, an L-type calcium channel blocker. We tried these and other treatment approaches, in order to avoid neuroleptics, and we found we could succeed most of the time.

TB: So, you tried to avoid the use of neuroleptics because of concerns of tardive dyskinesia?

RP: Yes, during the medication free periods, when we were trying to contain patients, we used either seclusion or wet sheet packs. As our studies and interventions progressed, we began treating the patients earlier and earlier, and the need for wet sheet packs fell by the wayside.

TB: This was, in 1970, and instead of giving them chlorpromazine or haloperidol, you used wet sheet packs, right?

RP: Right.

TB: And seclusion?

RP: Yes, both.

TB: And, you were waiting until lithium started to work?

RP: Lithium or other experimental drugs, like carbamazepine, valproate, nimodipine, and lamotrigine. We got some very excited manic patients through the medication free periods with these measures.

TB: How often did you use ECT?

RP: We used ECT about once or twice a year.

TB: So not frequently?

RP: Not very frequently. But we were always struck with how effective and rapidly ECT worked in patients who failed to respond to everything available at the time.

TB: So, you were impressed with ECT?

RP: Early on I was impressed. It was only in recent years we began to see more equivocal responses in some patients to ECT. Our findings were like those of Harold Sackheim's group, who achieved an eighty percent response rate in patients who are relatively treatment naive, but only a 50% response rate in those who are treatment refractory. Our patients were pan-refractory, so ECT has lost its halo. We saw some patients become tolerant to the therapeutic effects of ECT, and some patients had severe memory problems. The other problem with our bipolar patients was that many of them were rapid cyclers, and even if they had a good response to ECT, we still had to figure out what to do next in preventive psychopharmacology. So, we tried to come up with a pharmacological regimen on which they could go home for long-term maintenance.

TB: Rapid cycling is a relatively new concept. Could you define it for us?

RP: Dave Dunner came up with the category in the early 1980's. He defined rapid cycling as more than four episodes per year and found these patients were less likely to respond to lithium. We saw more and more patients who had four episodes per year. We also began to see ultra-rapid cyclers who had four episodes a month. With Keith Kramlinger and Mark George, we wrote papers on ultra-rapid cycling and ultradian cycling. We were seeing patients with classic manic-depressive illness switching many times within a single day. It turns out that the cycling spectrum is on a continuum, with no distinct cut off at the traditional marker of four per year.

TB: What was the proportion of rapid cyclers among the patients you had?

RP: It was 15 percent in the 1970's; and now, at the end of the 1990's, it is 75 percent in patients who come to NIMH. This is probably why we have to discharge them now on regimens involving

many more medications. Patients in the more recent cohorts have earlier onset of illness, more time depressed, and more rapid cycling prior to being included in our studies. So they had all sorts of negative prognostic characteristics.

TB: So, you are getting more severe patients than before.

RP: Right. The question arises, is this due to better treatment of patients in the community, as a result of which we are getting only the most refractory patients, or is the same thing happening in the community? I think it's a bit of both, as Myrna Weissman and Elliot Gershon have demonstrated a cohort effect. The age of onset for unipolar and bipolar illness is moving earlier and the incidence or prevalence is moving higher in every generation since World War I. Earlier age of onset of affective illness, higher incidence of rapid cycling, and treatment resistance are more frequent than before also in the general community.

TB: How many patients do you have on your unit?

RP: We only have twelve beds; it's a small unit. We had to make a choice whether we were going to try to do acute studies with a high patient turnover, or study fewer patients longitudinally. From the beginning, we decided to look at the long term effects of treatment. We wanted to figure out what was happening over time, how we could slow the progression of the illness and deal better with people who were treatment refractory. We wanted to see if they didn't respond to X, whether they would respond to Y or Z, or the combination of X, Y and Z. It turned out that treatment with complex combinations, especially in the more recent cohorts, was necessary. Mark Frye wrote a paper showing that we needed more and more poly-pharmacy to get the same degree of efficacy, and this was running in parallel with patients having faster cycling, earlier age of onset, and more time depressed prior to coming to NIH.

TB: So, the natural course of the illness has changed?

RP: To some extent there is sensitization or kindling effects in the course of untreated illness. That notion was put forward first by Emil Kraepelin. He noted that recurrences were coming faster and faster with shorter well intervals; that initial episodes were triggered by psychosocial stressors, and then, with enough recurrences, they started automatically. Those two fundamentals of the sensitization-kindling hypothesis were described by him, at the very beginning.

TB: You were trying to get information on the natural course of manic-depressive illness before it was re-named bipolar disorder?

RP: We tried to get descriptions of what the illness was like and how it evolved over time. Since we were looking at the long-term course, we got very interested in descriptions of the illness before there were good treatments available, to define the naturalistic course. We found our treatment refractory patients were having the cyclic acceleration Kraepelin described, which occurred despite the medications they were given.

TB: In which edition of his textbook did Kraepelin describe the cyclic acceleration we are talking about?

RP: His book published, in 1921. He described everything anybody could want to know about the natural course of manic-depressive illness. And we have seen everything Kraepelin described. Every time we thought we saw something new, we went back to the book and saw it was perfectly described seventy years before.

TB: Did you find the bipolar population a homogeneous group?

RP: We decided to take a very agnostic approach to see what the illness told us. Kraepelin did some charts on his patients and showed that episodes were totally chaotic and unpredictable. However, as an overall pattern, he found episodes would occur with shorter and shorter well intervals between each successive episode. So, we decided that the best thing to do was to adopt a Kraepelinian type of mood charting to more precisely map the course of illness of our patients.

TB: You were charting the mood of patients on your unit?

RP: We did very detailed mood charting, rating patients every day.

TB: What were you rating?

RP: Mania and depression severity, based on the degree of functional incapacity; how much they affected patient's social, educational, or occupational functioning. They were rated mild, low moderate, high moderate, and severe, in terms of incapacity associated with their mania or depression. And, with these daily ratings, we could, for the first time, accurately describe the precise course of illness. Bipolar illness is the most pleomorphic illness in psychiatry. You can have all patterns, all frequencies of both mania and depression. That's one of the reasons bipolar illness is so understudied relative to schizophrenia; the methodology is difficult because of the tremendous heterogeneity. We tried to describe the course of illness and its variations, rather than arbitrarily deciding an episode had to be two weeks or it wasn't an episode. We saw patients going manic and being in seclusion for one or two days and then being almost catatonic and depressed

for another two days. These patients would not meet classic criteria for an episode but it was a clear-cut all or none phenomena.

TB: You didn't stick with DSM criteria?

RP: We did comply with it, but once those criteria were met, we followed patients carefully to find what the real variations were. This is like the story of recurrent brief depression, where Jules Angst and Stuart Montgomery pulled the concept together, because DSM wouldn't allow you to diagnose a depressive episode unless it lasted two weeks. They found these recurrent brief depressions, just as we found recurrent brief manias. We also found fast patterns of mood switches, even within a day, tended to occur late in the illness. So, sensitization has been validated in the literature, by us and others, just like Kraepelin described them. The best data for validating the episode sensitization effect are from Kessing and colleagues, who looked at it in the Danish case registry in more than 20,000 unipolar and bipolar depressed patients. They found the rate of relapse and the latency to relapse were directly proportional to the number of previous depressive episodes. So, the notion that episodes sensitize to further and faster recurrences is definitely supported in the literature. The other fundamental Kraepelinian type of sensitization is that initial episodes are triggered by stressors but, after frequent episodes, they can occur on their own, was elegantly documented in unipolar depression by Ken Kendler. In 1992, I did a literature review on all of the studies that looked at stressors as a function of number of episodes. Kendler has shown that over the first 7 to 9 episodes of unipolar depression, stressors are involved as triggers to a successively lesser degree and, after that, stressors don't seem to be necessary precipitants anymore. The relationship between stressors and the occurrence of episodes plateaus after the first 7 to 9 episodes. So, both the stress sensitization and the episode sensitization concepts we derived from the cocaine sensitization rodent models, seem to hold in recurrent unipolar and bipolar illnesses.

TB: The concept of bipolar illness in the German literature is not restricted to manic-depressive illness but includes other illnesses. Did you have any interest in those?

RP: We looked at some of those, for example periodic catatonia that Gjessing described, but decided to just take the illness forms and see how they went along with different clinical phenomena and response to treatment. The DSM confused the issue, when they used the term mixed states. Mixed states can either be extremely fast variations in mood or more continuous

dysphoric mania. You can differentiate which part of mixed states is ultra-ultra, rapid cycling, like back and forth switching, within minutes to hours, ultradian cycling, and which is dysphoric mania. The cycling can be between severe depression and either euphoric or dysphoric mania. With our rating instrument, the NIMH Life Chart Method (LCM) you can handle all those concepts, descriptively.

TB: So, you collected all the information you could?

RP: We hope we did.

TB: That in itself is a major contribution.

RP: The NIMH-LCM is one of the more important contributions for both prospective research and clinical care. When I see patients I have them do daily life charts. When I do rounds on the patients on the unit every Monday morning, the first thing I say is “Hi, how are things going?” and I ask to see their mood chart. In this way, the patient and I can be in synchrony in an instant about where their mood is, how severe it is, and whether they’re improving or not. I don’t need to spend the first ten or fifteen minutes, to interview them for finding out about that information. We know immediately, and then we can get to more important issues in the short time available for rounds. We can discuss and think about what the alternative approaches are and how to deal with a patient’s illness. I ask all my patients to chart their mood on a daily basis and bring that in, so we can treat their residual symptoms.

TB: On how many patients do you have data?

RP: The NIMH inpatient cohort we have good retrospective and prospective life charts on is about three or four hundred patients. We now also have a collaborative outpatient project that is another nine hundred patients.

TB: That’s quite a number. How do your findings compare to those of Paul Grof?

RP: Paul Grof was one of the first to show the sensitization phenomena in recurrent unipolar patients, where the episodes got closer and closer together. He also has some unique cohorts of highly lithium responsive patients he’s been able to garner over the years. He studies lithium responsive patients and keeps them, as opposed to the NIMH, where we rarely see them.

TB: His population and yours are different?

RP: To some extent they are. I get more and more impressed with the heterogeneity of the illness and that some people are lithium responsive, whereas others are not. Some of this is going to get

sorted out when we have the right combination of clinical, physiological, and SNP profiling for treatment response.

TB: Paul Grof spent a couple of years at NIMH. Was he working with you?

RP: He worked closely with Fred Goodwin, but I got to know him later.

TB: What about Jules Angst and his data?

RP: Same thing. He chose to look at the illness, both in detail and longitudinally and now has a wonderful cohort of patients in which he has studied all the illness variations. He thinks that some five percent of the general public consists of patients in the bipolar spectrum. It's not just the one or two percent of bipolar I and bipolar II, but there's a whole spectrum of patients he can identify. He counts recurrent brief hypomania in variations of the bipolar spectrum. Angst broadened the concept, like Hagop Akiskal did, and has the data to support that. What's so beautiful in his cohort is that he's got longitudinal prospective data. TB: What about Mogens Schou, what kind of data did he have?

RP: Gorgeous data, and when British critics said lithium really didn't work, Schou went back and did other studies which reconfirmed lithium's efficacy in long term prevention of manic and depressive episodes

TB: What happened with his cohort of patients? Who is following them now?

RP: I don't think anybody is in that same way, but Per Vestergaard is following some of his patients.

TB: What happened to Paul Grof's cohort after he moved from Hamilton to Ottawa?

RP: I don't know.

TB: Was David Dunner at NIMH during your time?

RP: No, he was at NIMH right before me.

TB: He became known for coining bipolar II disease?

RP: Yes.

TB: Was the work you did with John Carman followed up?

RP: We measured calcium in plasma and spinal fluid and found it was elevated in depression. Ten or twelve years later, with Peggy Pazzaglia, we began to study calcium channel blockers. We were impressed with reports that verapamil, the L-type calcium channel blocker, was effective in mania in many small double blind controlled-studies, but when we saw that no one ever used it in

spite of the positive data, we thought that there must be something wrong. So we decided not to study verapamil, but instead studied the dihydropyridine calcium channel blocker, nimodipine, which seemed different from verapamil by having an anticonvulsant action. Nimodipine has effects on dopamine release and blocks cocaine hyperactivity, whereas verapamil does not. Nimodipine is also positive in animal models of depression, while verapamil is not. We gave nimodipine to our treatment refractory bipolar patients and found it did have effects in very rapid cycling and ultra-rapid cycling cases, on both the manic and depressive phases. The dihydropyridine calcium channel blockers are definitely worth a further look in both phases of bipolar illness.

TB: Do you think that nimodipine works also in treatment refractory depressed patients?

RP: Possibly. The problem with nimodipine is it's only approved for subarachnoid hemorrhage; treatment in daily doses, as high as 400 to 500 milligrams, would cost something like twenty-five thousand dollars a year. We think the other dihydropyridines, like isradipine and amlodipine, may be equally effective and less expensive.

TB: So you think the dihydropyridine calcium channel blockers are more suitable for treating bipolar illness than the other L-type calcium channel blockers?

RP: We've crossed a few patients over double blind from nimodipine to verapamil and they didn't remain well. They'd break through with depression and when we switched them back to another dihydropyridine such as isradipine, they would regain a response. So, even though there are few systematic data, I might try amlodipine, in those who were nimodipine responders or couldn't tolerate lithium and were switching moods within 24 hours, because it has a long half-life and can be dosed on a once daily basis.

TB: Would you consider calcium channel blockers an alternative treatment of lithium? RP: Yes, particularly for good lithium responders who are intolerant to lithium. Yet, they are typically not high up in the treatment algorithm. I would usually attempt to use several other mood stabilizers and combinations prior to using nimodipine.

TB: So, you would use combinations as a first alternative?

RP: Several drugs in combination or an atypical antipsychotic, if needed. I would use mood stabilizers and more mood stabilizers, even thyroid augmentation, antidepressants, and atypical

antipsychotics and then, somewhere further in the treatment sequence, calcium channel blockers might fit in, but not very early, except for those with ultradian-cycling.

TB: Okay.

RP: A patient came to me, who was a flutist, on lithium and doing beautifully, but she had a lithium tremor and couldn't play the flute as well as she would have liked. Every time she lowered her dose of lithium, she'd start to relapse. But now she's done equally well on calcium channel blockers as a supplement to her lower but well tolerated dose of lithium. It's people, who are cycling in an ultradian pattern, or can't tolerate lithium, who are the ones I use calcium channel blockers on.

TB: Was propranolol tried in your flutist to control her tremor?

RP: Yes, and it didn't work.

TB: Do you have data on drug combinations?

RP: No, there is almost no systematic comparative data in the field on drug combinations, and that's a problem. Everybody is now using complex combination therapies, three to five drugs on the average, but it's not like cancer chemotherapy where they know one combination works better than another, based on controlled trials. We don't have those kinds of systematic data on combination therapy in this field, partly because of controversy about what's the best methodology. Because of the variability in bipolar illness, it's very difficult to have treatment studies funded by the NIMH. Since Bob Prien's studies twenty-five years ago, Joe Calabrese's on prophylaxis are the first studies NIMH has funded in the area. It's a catastrophe! There is a need to study complex combination therapies and how to put them into appropriate algorithms. There needs to be a methodology to figure out better treatments for patients.

TB: Are you trying to develop a new methodology?

RP: I'm trying to find reliable and valid markers of the illness and ways of evaluating treatment response, so we can confirm what works and what doesn't. We have to start doing clinical trials of combination therapy systematically. That's beginning to be done in our Bipolar Collaborative Network and by a few of the drug companies, who are finally doing add-on studies. All of the new anticonvulsants have been FDA approved as add-on's, for refractory epilepsy. But, in psychiatry, we keep insisting on monotherapy, even though it doesn't work well for the vast majority of patients with bipolar illness. That's an area where we need more data.

TB: Would you like to say something about your findings with brain imaging?

RP: We're finding that some unipolar and bipolar depressed patients have the classic frontal hypometabolism on PET scans, but others are hyperactive during depression. These two types of patients respond differentially to high frequency vs. low frequency rTMS. High frequency rTMS increases toward normal the low baseline patterns of prefrontal activity, and conversely 1 Hz or low frequency rTMS drives down the pattern of prefrontal hyperactivity. When patients are matched to the right frequency of rTMS, according to baseline activity on PET scan, this may help in prediction of a positive response. That's one thing Dr. Andy Speer is doing, mostly in unipolar patients, but also in some bipolars.

TB: You have recently turned your unit over to one of your associates? Are you still involved in research on the unit?

RP: I am more involved in design, analysis, and interpretation of the studies, but I don't do the rTMS or brain imaging procedures.

TB: What is your position at NIMH?

RP: I went from Unit to Section Chief to Acting Branch Chief and, for the last twenty or so years, I've been Chief of the Biological Psychiatry Branch, the clinical equivalent of a lab chief. The Biological Psychiatry Branch used to be an enormous lab, under Biff Bunney. When I took over, it got considerably smaller and now just one clinical focus, on rTMS. We are not doing anymore animal laboratory work I'd been doing with Dr. Susan Weiss. She'd been doing all the kindling and cocaine sensitization work, but that lab is closed, as well as our neurochemistry lab.

TB: So the group has reduced in size?

RP: Yes, and now, it's just a small clinical group with a total of eight people; one physician, a social worker, and several research assistants and secretaries.

TB: What would you consider your most important contribution in the field?

RP: My important contribution, I think, is around the longitudinal view of recurrent bipolar affective disorders, as often following a kindling-like course. The idea that episodes can speed up over time and one can get sensitized to stressors and substances of abuse, such as cocaine, and that if you intervene early with effective prophylaxis, you may be able to ward off the adverse consequences in these otherwise recurrent illnesses. That's what I'd like to do next, treat bipolar illness in kids early, to see if it makes a difference over the course of their life. The notion of

affective recurrences initiating a downhill course emphasizes the importance of episode prevention, so early treatment maybe more important than anything else.

TB: Do you mean by starting treatment in children?

RP: It would be good to do in those with childhood onset.

TB: What is the current status in that area of research? Have you done any studies in children?

RP: We designed a study for very high-risk bipolar kids, who have bi-lineal pedigrees. When they become symptomatic, even before they get the whole full-blown illness, one should consider treating them. We did a survey that asked parents whether they would volunteer their kids for that kind of study, and they said they definitely would. But, so far, we haven't been able to put the study together.

TB: Is there any other area of research you have been involved with we haven't touched upon?

RP: No. The central theme of my research is how to treat patients with bipolar illness more effectively. This idea of early intervention would be a new territory, driven by patient needs. Early intervention would fit in with the theoretical overview of the kindling hypothesis that the illness can be progressive. If you could treat early, you might save people a tremendous amount of grief, like with malignancy. If you take it out early, before it metastasizes, it's a lot easier to treat.

TB: Do you remember what your first publication was?

RP: An article with Joel Kotin, in which we reported that most patients with depression who came to our unit were under-treated. The disturbing thing is, even though we do much better now, there are still a tremendous number of patients in the community who are not being treated for serious depression and, even worse, for bipolar illness. In our outpatient bipolar collaborative network, we're finding an average of ten years' delay between the onset of first affective symptoms causing dysfunction and the first treatment. The delay has horrendous consequences. Not only are people ill and suffering, but the continuous presence of symptoms may be making the brain more vulnerable to cell dysfunction and further recurrences.

TB: What was your last publication?

RP: The last one was a description of the illness morbidity of naturalistically treated bipolar patients. The first 253 patients in our outpatient collaborative network had considerable morbidity after one year of prospective naturalistic treatment. About two-thirds of patients in this cohort were still markedly impacted by their bipolar illness, despite being treated with an average of four

classes of pharmacological agents. In that paper, we also examined what were the predictors of who did well vs. who did poorly, and those with earlier onset and more and more prior episodes fared the worst.

TB: When did you get involved with ACNP?

RP: I was very fortunate that Fred Goodwin, early on, brought me to one of the ACNP meetings. I was like a kid in a candy store. I went to every session and thought everyone had new and exciting findings. The ACNP has always been the key meeting in my professional life and continues to be.

TB: When did you attend the first annual meeting?

RP: Probably in the late seventies or early eighties. It's a long time ago, but it's been a consistently wonderful experience.

TB: Have you been active in presenting papers?

RP: I have been a presenter or discussant many times, and always an interested and active participant.

TB: Have you been active in committees?

RP: I've been totally absorbed in clinical research, so I haven't been very active in the College. I was on one of the training committees getting young investigators to the ACNP, and now I am on the liaison committee.

TB: Weren't you the recipient of one of the ACNP research awards?

RP: I received the ACNP Daniel Efron Research Award a number of years ago, and it's one of the awards I'm the most proud of. To get the award from my colleagues was wonderful. TB: Any other awards?

RP: I got the A. E. Bennett Award and the Gold Medal Award from the Society of Biological Psychiatry, an award from the American Psychiatry Association, the International Anna Monika Prize, and several other prizes like that. It was also very meaningful to win prizes from some of the patient associations; the Klerman Award from the National Depressive and Manic Depressive Association (NMDA) now called the DBSA, and two NARSAD awards, one for lifetime research on bipolar illness.

TB: Do you have a family?

RP: A wonderful family; my wife, Susan, and a daughter, Laura, who married in September, right after the 9/11 catastrophe, and a son, David. Neither of my children wanted to go into

medicine. They're both teachers, which is great.

TB: Any other interest beside your research?

RP: I am a golfer. I played on the high school team and on an intramural college team, but I didn't quite make the Yale Varsity, but I was close, only two strokes away.

TB: Is there anything you would like to see happen in the field?

RP: I hope we can get over the current controversies about how bipolar illness presents in children, so we can treat them earlier and more effectively. A key issue, for both children and adults, is figuring out which medication works for which patient, and which combinations work best. It would be wonderful to have systematic data in those areas.

TB: Do you think we have progressed in your area of research during the past 30 years?

RP: In spite of the funding shortfalls in bipolar illness, the field has advanced remarkably from having lithium, neuroleptics, and antidepressants to a huge range of options. All we have to do is figure out how to put them into play in the best way.

TB: And, you feel strongly that it would be very important to have better funding?

RP: Oh, yes, better funding for bipolar illness treatment research and somehow getting over the methodological issues so there are more NIMH funded studies. Even at the ACNP, there are four to five times more panels on schizophrenia than on bipolar illness, despite the greater prevalence of bipolar disease. Investigators get discouraged because of the funding shortfalls, so I hope that can change.

TB: Thank you very much for sharing all this information with us.

RP: Thank you for asking and listening to all these clinical treatment issues. And thanks to the ACNP for everything they've done for me, personally, and the field of mental illness research in general.

52. WILLIAM Z. POTTER

TB: This will be an interview with Dr. William Potter⁵⁴ for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College, in San Juan, Puerto Rico. It is December 8, 2003. I'm Thomas Ban. Let's start from the beginning; when and where were you born? Tell us something about your education.

WP: I was born on April 3, 1945, in Charleston, South Carolina. At that point, my father was still in medical school, somewhat older than the rest in his class. He had gone back to medical school during World War II, after working in the state public health service in South Carolina.

My mother's family had come from the south, and my father's family had been from Tennessee and North Carolina. My father did not like the strained race relations in South Carolina and when I was about four years old, he moved us to Ridgeville, Indiana, a small town of about a 1000 people. I was brought up in this small mid-western town, although all my family was from the south. My father was in partnership with an older doctor, who died tragically in an automobile accident two or three years after we arrived. So, my father became the only doctor for an area of many miles and would rotate back and forth between two county hospitals, 15 miles apart. As a child, I would ride with him to visit patients in their homes. My father's office, with my mother's help, also ran a pharmacy because there was no drugstore in the town. He diagnosed and treated patients and was doing lots of minor surgery. The pharmacy allowed him to charge patients very little; many weren't charged at all, except for the medicine. He was very much the country doctor. Seeing the way my father lived, both my older brothers decided they would not study medicine, but I picked up the idea medicine was important. The educational system in the town, where we lived was very bad, so my parents decided it would be good for me to have the opportunity to get a better education, and I was sent to a boarding school outside Cleveland, Ohio, Western Reserve Academy. It was a very good boarding school with sixty people in each year. A fifth would do extremely well and it was competitive. A lot of graduates from Western Reserve went on to East

⁵⁴ William Z. Potter was born in Charleston, South Carolina in 1945. He received his M.D./Ph.D. from Indiana University in Bloomington, Indiana while doing his research at the Intramural Research Program of National Heart and Lung Institute while doing a PRAT fellowship. He completed his psychiatric residency at Saint Elisabeth's Hospital, while continuing research at the Intramural Program of the National Institute of Mental Health in Bethesda, Maryland. He continued his research career at the Intramural NIMH, until he was recruited by Eli Lilly Pharmaceuticals in Indianapolis, Indiana. He was interviewed in San Juan, Puerto Rico on December 8, 2003.

Coast schools but I won a full scholarship to school in England for a year. There, I studied A-levels in history and became interested in philosophy. In the meantime, my father had been ill, so I decided to go to Indiana University on return from England. There, I was able to do my undergraduate work in a couple of years. About that time, the NIMH had been funding M.D. /Ph.D. programs and I was accepted for one. I had a vision of becoming a well-educated doctor, and I planned to do a Ph.D. in philosophy along with my M.D. So I was taking my pre-clinical courses for medical school, while attending courses in philosophy. I was a very good student in philosophy but they would not give me a fellowship because they knew I intended to become a doctor; it would be a waste of money. I thought this was not in the spirit of the program and went to my advisor, Lyle Beck, a very nice older gentleman in the Department of Pharmacology. When he learned about my problem, he said I could work in his department. So I did, and I earned money washing dishes in the Department of Pharmacology. They also involved me in experiments measuring insulin levels, using a radioimmunoassay technique.

TB: When did this happen?

WP: This was back in the 1960s. Radioimmunoassays had only been out for a couple of years, at the time, but I got lab experience and handled pipettes pretty well. They suggested I do a degree in pharmacology, so I did. This is how I got into pharmacology.

TB: What year?

WP: In 1966, I switched from philosophy to pharmacology, and later, received my master's in pharmacology. My early research and first papers were on the effects of hydrazine that was used originally as rocket fuel but there were concerns it might be a hazard for astronauts exposed to it. The research was prompted by reports hydrazine produced dramatic changes in blood glucose in rats. In the course of that research, I learned how to cannulate rat arteries. That was not a routine procedure so I had to work out how to do it. I learned you could work things out for yourself in the lab; that you could develop new assays just by reading papers. By the time I received my M.D., the Vietnam War was on and I had the choice to be drafted or get a NIH fellowship in the PRAT program.

TB: When was that?

WP: In 1971. I remember interviewing with BB Brodie, who asked what I was interested in, and I explained some of the research I did and how I enjoyed it. Then he went on an incredible riff

about coming back from Australia, where sheep were dying of liver failure, and he got to thinking about what might be going on. To make a long story short, his view was there might have been an active metabolite being formed from a substance causing liver necrosis. I said, Dr. Brodie, I don't know anything about liver necrosis. "Good," he told me, and literally picked up the phone to call the secretary of the PRAT program and said, "Bill Potter is coming to my laboratory." I later became very involved in NIMH's PRAT Program and learned about the rules for bringing people in. He was highhanded, but if you were BB Brodie, you could be like that. And working in Brodie's lab on how active metabolites of drugs can cause liver necrosis was an incredible experience. My first decent papers were all related to acetaminophen-induced hepatotoxicity. It was a classic series of articles, which are still frequently cited. A group of us with a guy called Jerry Mitchell were involved. Brodie's name was on all of them, and sometimes Jim Gillette. I also remember that under the pressure of meeting presentation deadlines, we had difficulty to reproduce acetaminophen induced toxicity in the rat. You could convince yourself the findings were there, but we had to heat up the acetaminophen, which didn't get in the solution very well, ram it down the rat's throat, and sometimes you would get results and sometimes you wouldn't. This made me nervous, being new, because you wanted to have clean results. About that time, and I'm pretty sure it was BB Brodie who said, why don't we look at other animals? I will never forget the experiment injecting acetaminophen in a series of rabbits, guinea pigs, mice, and hamsters; on autopsy we saw nothing in rabbits and guinea pigs, but when we opened up the hamsters and mice, the livers were white. Working in Brodie's lab taught me to make an experiment work one needs a good animal model and very robust endpoints. In that lab, I would also try to show chlorpromazine might be activated to something that causes hepatotoxicity, but that turned out to be due to a different mechanism. During that time, I realized I wanted to take laboratory science and apply it to developing new treatments; I also decided to do a residency in psychiatry.

TB: What year was that?

WP: In 1974. After a three year PRAT fellowship, rather than staying in the Heart and Lung Institute, I entered psychiatric residency at Saint Elisabeth's Hospital. I forgot to mention my Ph.D. dissertation was done at the National Heart and Lung Institute with the cooperation of Roger Michael. Indiana University allowed me to do my Ph.D. work at NIH.

TB: You got your Ph.D. from Indiana University but did the work at NIH.

WP: Yes. The Public Health Service also allowed me to start my residency in psychiatry at Saint Elizabeth's Hospital, and continue doing research at the NIH, which, by that time, became the National Institute of Mental Health (NIMH).

TB: When was that?

WP: In 1976. So, I did not return to the Heart and Lung Institute but to Fred Goodwin's branch at NIMH. I was, for the next 20 years, part of the Intramural Program at the NIMH in a number of different roles. First, I was in Fred's branch, and then I got a section of clinical pharmacology that was created because I was trying to do bridging research from studies in animals into humans. Part of the time, my position was supported by the National Institute of General Medical Science. I was coordinating the training of both clinical pharmacologists and psychopharmacologists at NIH. So, I supervised individuals who were clinical pharmacologists in many of the other institutes, as well. But my personal research interest remained in clinical psychopharmacology. That is, how I got involved with the ACNP.

TB: In what year?

WP: 1978 was the first time I came to a meeting here, in Puerto Rico. The focus of my work in clinical psychopharmacology covered all of the classic questions in pharmacology, such as how the blood concentration of a substance relates to clinical effects. That has been extraordinarily elusive because, unlike in rats with necrotic livers, our outcome measures for depression, schizophrenia, anxiety disorders, and manic depressive illness are not very precise and do not lend themselves well to looking at simple concentration-response relationships, nor does the time course of effect. I learned that early on. However, during the 1970s, there was a burst of activity hoping that measuring concentrations of drugs would greatly improve therapeutics. Retrospectively, the fundamental lesson learned as we appreciated the variation in drug metabolism, was that many, many patients were under dosed. The general rule that emerged was that it was important to use higher doses to achieve therapeutic effects. This may seem obvious now, but back then a lot of people were being treated, particularly in depression, with subtherapeutic doses. The lesson of finding the right dose has been well learned, although it is still not well done. Post-marketing experience with many of our new antidepressants and antipsychotics indicates the marketed dose is not always the right one. Once I became comfortable with classic pharmacological/pharmacokinetic measurements, I became interested, as did many

other people at NIMH, heavily influenced by Fred Goodwin, in manic depressive illness, a robust clinically striking condition, in which you had multiple phases of the illness. I became interested in the work on catecholamines by Irv Kopin's group, and also inspired by Julie Axelrod's research. It provided an opportunity to explore whether the biochemical theories related to mental illness that were very popular, could be proven in humans.

TB: Which theories are you referring to?

WP: The biochemical theories, then current, had to do with an abnormality of catecholamine metabolism, a "noradrenergic depression" or an abnormality of indoleamine metabolism, a "serotonergic depression." It was thought that antidepressant effects could be produced with selective serotonin reuptake inhibitors (SSRIs).

TB: What years are we talking about?

WP: Mid to late 1970s. There had already been data coming out of Sweden, using a fairly selective serotonin uptake inhibitor called zimelidine, in the treatment depression. The research that led to SSRIs was laid out by people like Arvid Carlsson. Although Brodie and Costa had been focused on serotonin, it was Arvid who first provided solid evidence that tricyclic antidepressants influenced the serotonin system. To make a long story short, we did what was to me the most important formative clinical experiment for my development, by comparing zimelidine, from Astra Pharmaceuticals in Sweden, with the most selective norepinephrine reuptake inhibitor we could find. The hypothesis was, you would get selective effects on serotonin and norepinephrine metabolism. The results were you could not distinguish very clearly between the two. Each drug, after several weeks of administration, influenced both norepinephrine and serotonin metabolism. Our findings led us to speculate there must be interactions between the norepinephrine and serotonin systems that were important in terms of downstream events. It was a very important experiment, from my point of view. I learned that one could not follow a relatively simplistic model in psychopharmacology, in which, if you know the pre-existing biochemistry, you would have a specific biochemical treatment for a particular subtype of psychiatric illness. It indicated a simple approach to biochemical sub-typing was not feasible, most important would be to understand the mechanism of action of psychiatric drugs. In the next decade of my career, I studied how psychotropic drugs, in therapeutic doses, affect more subtle pathways than norepinephrine and serotonin. I was especially interested in the effects of lithium on signal transduction.

TB: How did you get from NIMH to Lilly?

WP: When Steve Paul left NIMH, in the early 1990s, he suggested the best opportunity for research from bench to bedside might be in the pharmaceutical industry that has the enormous resources necessary to carry this off. So, in 1996, I went to work in the research laboratories of Lilly. The era we are now entering is going to be putting research at NIH, in large academic consortiums, and in industry together, creating information in databases with proteomics and of course genetic measures. The American College plays a huge role in providing a forum to bring us together with different ideas about how to achieve this objective. The annual meetings of ACNP provide an opportunity to be in touch with the latest evolving science on a regular basis. It is in these meetings, the best conversations take place in terms of figuring out how to create the ideal interaction between government, industry, and academia.

TB: Let us get back to your research. You entered psychopharmacology by becoming involved in drug metabolism and pharmacokinetics. Could you put that research in perspective for us?

WP: Research in those areas is still extraordinarily important. Controlling your dose in your preclinical experiment is a huge issue, even now. When you give 10 mg per kilogram of a substance you get more or less the same exposure across your inbred rats. In humans, that is not so. Pharmacokinetics is core to controlling for variants, that is a given. One takes that as part of life. What hasn't been so easy is modeling the relationship between pharmacokinetic and pharmacodynamic findings. It has been extraordinarily difficult in the brain to relate concentrations to systematic changes. This has to do with difficulty in understanding changes in interacting systems, where you have a time element; when we look at biochemical outputs we are looking at points in time, not at a constant curve, where there is stability unless we are looking at something like receptor occupancy. That is the only area where PK/PD works out really well.

TB: That is very important for neuropsychopharmacological research.

WP: It is. When we worked at Lilly on antidepressant potentiation with pindolol, we had difficulties interpreting our findings because nobody had defined appropriately in humans the relationship between pindolol concentration and occupancy of the 5HT_{1a} receptor. The hypothesis was that blocking 5HT_{1a} receptors would potentiate the effect of serotonin uptake inhibitors. When people looked at the findings, they concluded the doses of pindolol used in those clinical studies probably only hit receptors. The doses used only achieved 25, 35, or at most 40 percent occupancy

of the 5HT_{1a} receptors, instead of full or at least 90 percent occupancy. Despite the tens of millions of dollars spent in that research, the hypothesis has not been properly tested. I can give multiple examples of similar cases. If we do our experiments right, we will be able to greatly increase our success rate. We should be able to do that now with the employment of brain imaging technologies.

TB: Do you think it is feasible?

WP: It is becoming increasingly feasible with ligand development. We have already developed ligands for the norepinephrine transporter with people in Upsala, Sweden, and we are moving ahead with ligand development so we should be able to use PET or SPECT in our drug development programs. An exciting aspect of this research is that it is done in collaboration with the NIH. We are co-grantees with both Columbia and Hopkins in developing ligands for novel targets. We are finding ways to work together and I am convinced this will greatly improve our hit rate in developing novel therapeutics.

TB: So you hope to develop collaboration between government, industry, and academia in this crucial area of research?

WP: Right.

TB: Earlier you said one of your important findings was that norepinephrine and serotonin reuptake inhibitors might not be as selective in their mode of action as we think.

WP: Yes, and we have to approach questions very differently from the rather simplistic model we had been using. At the time I did that research, the prevailing theory of antidepressant action was β -receptor down regulation, and Fridolin Sulser was one of its great champions. We were all trying to show, using peripheral lymphocytes, or whatever, to find indirect ways of measuring β -receptor down regulation in humans. All that was far too simplistic; eventually it became apparent we have to understand the full cascade of events, including the coupling of receptors to G-proteins and second messengers. During the 1980s, it became possible to incorporate all molecular pharmacology done before then and, by re-looking at the chain of events, we learned there was a far more complex series of adaptive events that followed the primary action of drugs. Many of those events could be shown in vitro and in cell cultures without invoking more neurotransmitters hitting the receptor. In the period from the mid-1980s to almost the present, we have been retrenching and learning more about how these complicated systems really work and redefining the downstream biochemical effects of drugs. The question is whether we would be able to profile

those effects in sufficient depth to distinguish different actions across individuals and then to relate that back to treatment response. So we are going back to the strategy of the 1970s, but at a higher level. At that time, we simply didn't have the tools to do it well.

TB: What was the impact of your findings that, down the road, serotonin and norepinephrine reuptake inhibitors follow a common path in their mechanism of action?

WP: A great number of people insisted there was a norepinephrine and a serotonin depression and we should be able to separate them. Others went along. One of the biochemical scientists at Lilly told me, it was the most important clinical paper he had seen; it has had a large impact in the way people think by supporting a shift in focus from single neurotransmitters to interacting and coupling systems. What I viewed at the time as a very simple and obvious experiment has had a substantial impact.

TB: So, you think it has had an impact on the thinking of people?

WP: It changed people's thinking and strategies at Lilly. I am sure it has been the most impactful single paper I was ever involved with.

TB: Would it be correct to say that the biochemical measures we used have not contributed so far to the classification of depression?

WP: Right. We have remained as a field of psychiatry, in a descriptive phase. Most of what people put forward as biochemical hypotheses are far too simplistic because we are not adequately describing, in objective terms, the state of individuals. We can do that partly with behavioral and functional measures, but rating scales have their limits. To subdivide people it seems clear we need a combination of genetic, biochemical, and other objective functional measures. Brain imaging measures have been evolving continuously but the initial enthusiasm of fitting brain imaging measures to drug development has to be balanced by the reality. Anything beyond receptor occupancy still has not shown predictive, reproducible, dose response relationships. The pharmaceutical industry, the NIH, and other authorities, are funding the employment of brain imaging techniques in research for studying drug effects, but the databases are only just emerging. Many of us hope proteomics might open up development. It is already applied in the cancer field with some early success but it is too early to say what it will deliver.

TB: You believe one would need to integrate findings from various areas of research in order to describe individuals in sufficiently objective terms for clinical psychopharmacological investigations?

WP: For doing clinical psychopharmacology well, one is going to need a matrix, a team with investigative skills that go beyond what any individual scientist can adequately master in terms of fully understanding the methodologies of different disciplines and the limits of each of them. For successful drug development in such a complicated system as the brain, it is extraordinarily important we find ways to get people with the right skills to work together. I am hoping, over the next few years, to find ways to do that.

TB: Are you involved in any project in clinical psychopharmacology in which people with the “right skills” work together?

WP: We are trying to develop such a project with the National Institute of Aging, looking for new drugs in Alzheimer’s disease. This will be the biggest joint effort ever put together, at least for the CNS field, whereby industry will put in upwards of 20 to 30 million dollars for a five year prospective study of minimal cognitive impairment preceding to Alzheimer’s because, if you diagnose MCI the right way, about 80% go on to get Alzheimer’s. Imbedded in that project will be a complex combination of imaging, MRI, PET scans, and cerebral spinal fluid studies of proteomics. The study should start in early 2005; so we are still in the planning stages. This is very exciting to me, because it is the sort of research that needs to be done if we are going to find breakthrough treatments for important CNS diseases.

TB: What about research in schizophrenia and bipolar disorder?

WP: We would have a concerted effort in bipolar disease before we go after schizophrenia. It is interesting that we are back to the recognition that schizophrenia is, in the broad sense, a disorder in thinking including cognitive function. Even if you successfully treat the positive symptoms, it is obvious people are left with substantial cognitive impairment. The NIMH, working with FDA and industry in the MATRICS Project, is recognizing the need to go after cognition in schizophrenia. I am very excited to be part of that project, trying to sponsor the development of novel scales for assessing cognitive disturbances in schizophrenia.

TB: The projects you are talking about will generate lots of data.

WP: One of the other exciting opportunities I have recognized since coming to industry is that it has the capability of generating enormous data sets from which one could extract information.

TB: Any big project planned in bipolar disorder?

WP: Bipolar disorder would be one area where, if we all invested enough, we might be able to find more compelling patterns of biochemical dysfunctions we could relate to treatment, but right now there is no unified program or approach doing that.

TB: Don't you think that before undertaking such expensive projects, it would be important to define the diagnostic populations better than in current consensus-based classifications?

WP: I still believe the classic bipolar phenotype remains one of the clearest defined. Genetic research keeps supporting there is something there. Genes associated with risk for psychosis coupled with other susceptibility genes seems to confer the bipolar phenotype. As genetic research evolves, maybe this will become clearer, and we will identify people at risk, understand the biochemical pathways susceptible to alterations under the genetic circumstances, and do something that is more than palliative. Those are dreams but one can see a path.

TB: It is a long journey we covered from your first research project as a student on hydrazines.

WP: I was a young graduate student who knew nothing about science, and who never thought of himself as a scientist. I was studying philosophy. But then I learned the process of generating questions and found testing them in research very gratifying. It is like a chess game. It has the advantage over philosophy that you can propose a question and test it. Unfortunately, in philosophy, you could never test your core questions.

TB: What was your primary area of interest in philosophy?

WP: Logic with an underpinning in ontology.

TB: You probably learned from philosophy that you have to start research by formulating a testable hypothesis.

WP: You formulate it, and then you test it. I came from a background where pursuing truth and doing the right thing was very important. I have always felt you had to use knowledge the best you can, like translating new knowledge into new treatments. I have always wanted to be part of those who are translating new biological knowledge to better treatments. All through my professional career, I have been interested in applying what I learned in pharmacology to more rational drug development. My role is to bring together and implement things which allow us to develop better treatments, not just "me too drugs."

TB: You mentioned you did some research with lithium?

WP: We did a series of work to try to understand the mechanism of action of lithium; from a learning experience that was tremendously important although we didn't find it. People are still working on that.

TB: We talked about briefly about you training in psychiatry.

WP: My psychiatric training gave me the opportunity to have direct relationships with patients. I still see patients, believe it or not. All those years at the NIMH, in addition to the patients on the ward, I also saw patients outside.

TB: Do you still have a practice?

WP: Yes, even now. At the NIH I had a small practice in which I did a few hours a week, but I followed many people with complicated manic depressive illness or severe depression. I became very interested in the limitations of our ability to assess the condition of a patient. It was not until I went to Lilly, in 1996, that I had access to databases to look at some of the issues. One of the first things I did was to put together, with the help of David Debroda, meta-data sets. We have now the largest meta-data set of antidepressant trials ever put together. We also have a large data base on olanzapine. We are beginning to put together the meta-data sets and understand the extent to which measures do, or do not, reveal similar information over time. Being in a position to see how these scales perform, I think maybe we should invest in additional refinement of them. Scale development and validation are just as important as molecular studies.

TB: Let me switch to something completely different. When did you become a member of ACNP?

WP: It must have been early 1980s.

TB: Have you been active?

WP: Oh, yes.

TB: Do you remember your first presentation at an annual meeting?

WP: I don't remember but it must have had to do with pharmacokinetics. It probably was the prediction of steady state based on a single dose, because, working with Jim Gillette, I understood that from acute dose pharmacokinetics you should be able to predict a steady state. There were also misunderstandings about protein binding I dealt with. I was able to tell people to stop worrying so much about protein binding because it is only relevant for certain phenomena; people were misinterpreting its meaning and thought protein binding limited access to the brain. It doesn't. It

merely says something about how you should interpret total blood levels. I was also involved in presentations that dealt with active metabolites.

TB: What are you doing these days?

WP: My current activities are much broader, since I am involved in coordinating early development of drugs. What I am trying to do at Lilly, and more broadly in the field, is convince people to build into studies with CNS drugs documentation about the biochemical target they are hitting in humans. I'm also interested in finding ways to enhance signal detection and outcome measures in early clinical trials. I understand people like Don Klein say, if you had a drug that worked, picked your patients right, and measured them right, you should be able to tell in a small number of people whether the drug is useful or not.

TB: So you think it is important to enhance signal detection.

WP: I have been trying to convey that without enhancing signal detection, you waste your efforts in clinical trials. An example of the need for enhancing signal detection is buspirone. Since its introduction at least 10 and probably 15 pharmacologically similar 5HR_{1a} partial agonists and full agonists have been tested without any of them making it to market. We estimate probably a billion dollars has been spent to test these drugs. That is a lot of money but nobody knows the extent to which the doses used produced an effect in the brain. Not only have we spent all this money and not come up with anything, but we haven't learned anything either. This repeats itself several times over.

TB: What would you like to see to happen in the future?

WP: Real knowledge emerging. From an ethical view as a clinical investigator, you should hesitate going forward with a study, unless you can say you have learned something from the research about the mechanism of action of the drug you are working with. If you're using doses of drugs which, if the technology exists, don't show you are hitting your target, then you have omitted an essential component to your study. Then, if you have negative data from a study in which you tested a hypothesis, you should be required to share the data. This is not a game where you let another company go down the wrong path if you know it is the wrong path.

TB: You seem to feel strongly about this.

WP: I feel very strongly. We need to do something about that because it can happen.

TB: Anything else you would like to add?

WP: I think I have talked enough.

TB: Then, we should close this interview. Thank you for sharing this information with us.

WP: Thank you for the opportunity. It has been a lot of fun.

53. FREDERIC QUITKIN

TB: This will be an interview with Frederic Quitkin⁵⁵ for American College of Neuropsychopharmacology archives. We are at the annual meeting of the College in Hawaii. It is December 11, 2001. I'm Thomas Ban. Let us start from the very beginning; where and when were you born. Tell us something about your early interests, education, and how you got involved in the field.

FQ: I was born in Brooklyn into a middle class family, which had intellectual interests. My father was the product of the depression, so he didn't have an opportunity to do everything in education he would have liked. This was also true of my mother. My father was a real intellectual. My mother was also, but to a lesser extent. My father instilled the idea of doing research into me in a rather subtle fashion.

TB: Where did you go to university?

FQ: I was fortunate enough to get a scholarship to Princeton, which was a wonderful experience. It's a great university. Unlike other universities, undergraduates are required to write a thesis. As a biology major, I had to do a project to do with the effects of urethane analogs on viruses. I then went to medical school at Downstate. I had, without knowing anything about it, an interest in psychology and perhaps psychoanalysis. But I went to medical school and my first interest was in pathology, which I got tired of, then internal medicine, and finally, psychiatry. I decided routine cases in internal medicine would not be as interesting as routine cases in psychiatry. I went into psychiatry thinking that I would be a psychotherapist.

TB: When and where did you do your residency?

FQ: In 1963, I started at Hillside Hospital, where I was fortunate to meet Don Klein. I very quickly became disillusioned with psychoanalysis and felt that there was no empirical base to it. "Freud said it, so you should believe it," was the spirit at Hillside in the 1960s. Then I was exposed to the empirically-based research Don Klein was doing and developed an interest in psychopharmacology.

⁵⁵ Frederic Quitkin was born in Brooklyn, New York, New York in 1937. He received the M.D. degree at the State University of New York Downstate Medical Center in Brooklyn, New York. He completed his residency in psychiatry at Zucker Hillside Hospital in Glen Oaks, New York. He was interviewed in Waikoloa, Hawaii, December 11, 2001. Quitkin died in 2005.

TB: Didn't you get involved in research as a resident?

FQ: That's true. I got involved in research and I did a couple of studies.

TB: What did you do?

FQ: At the time, virtually all inpatients were diagnosed as schizophrenic. So one of the studies I did as a resident was a follow-up of a patient who had been suicidal for a year. After she was transferred to a State Hospital, she suddenly got better and left in 2 weeks. So, I planned a study Don Klein helped me with. He re-diagnosed everybody transferred from Hillside, which was a comfortable, pleasant place to be treated, to the State Hospital. The hypothesis was that the nonschizophrenics would quickly leave the State Hospital, whereas the schizophrenics he diagnosed would stay. The prediction was right. Clinicians labeled virtually all patients schizophrenic, so this had no predictive value.

TB: What did you do after your residency?

FQ: I went to a Doctor of Medical Science program run by an experimental psychologist, Dr. H. Witkin, at Downstate Medical Center. It primarily consisted of courses in how to do research. I had exposure to statistics and design, and in 1969, I went back to Hillside and got involved in psychopharmacologic research. There were three broad themes. The first theme consisted of studies involving the maintenance and prophylactic treatment of schizophrenic and bipolar patients. It was when lithium first came out. I was also interested in neurological signs of schizophrenia.

TB: What about the second theme?

FQ: After moving to Columbia, in 1977, I became interested in two areas; atypical depression and placebo response. Using the response to antidepressants, we showed that atypical depression did better on monoamine oxidase inhibitors (MAOIs) compared to melancholic patients, who did well on either tricyclic antidepressants (TCAs) or MAOIs. Our findings indicated a categorical distinction between the two diagnostic groups. Subsequent epidemiological genetic studies by others suggest atypical depression may be distinct genetically from melancholia.

TB: Tell us something about your research with placebo.

FQ: I was involved in identifying those with placebo responses to drugs. Sixty percent of depressed patients improve on a drug and thirty percent on placebo. The question was to identify characteristics of patients who got better on placebo. We found if you got better in the first two

weeks or had a fluctuating response, you probably were having a placebo response. The big difference was that improvement in the drug group occurred after the third week and later. It was convincing to see that those with a placebo pattern, randomized to drug or placebo, did well on either, whereas those with a “specific drug response,” did better on drug than those randomized to placebo. We published the findings in the *Archives* a few years ago. In another study with Remeron (mirtazapine), we virtually replicated our prior findings.

TB: What about the third theme?

FQ: I was interested in was the relationship of substance abuse, mood disorders, and self-medication. So I did several studies in this area and have shown that patients who had primary mood disorders and received antidepressants versus those who got placebo did better in terms of the way they felt and their substance abuse diminished. We did a similar study with outpatient alcoholics.

TB: What else did you do at Columbia?

FQ: I ran a depression clinic where we were fortunate to admit only people who were willing to go into a study in exchange for treatment for six months. During my stay at Columbia I have focused entirely on research in depressive illness.

TB: Wasn't your first research project at Columbia focused on the differentiation between atypical and other depressions?

FQ: That study went on for about 10 years. There were multiple different trials to make sure our findings were correct. We used our own criteria for atypical depression, which became the basis for a parenthetical modifier in the DSM-IV.

TB: Did your findings in atypical depression differ from the findings of William Sargent in the U.K.?

FQ: Sargent never spelled out his criteria. The prevailing opinion in the U.K. was that it was anxious depressives, who did better on MAO inhibitors. We analyzed our data and showed it made no difference whether the patients were anxious or not. Patients with reversed vegetative symptoms, even in the absence of anxiety, have a big difference in treatment response between MAOI and placebo.

TB: Didn't you publish on the prophylactic treatment of schizophrenia at Hillside?

FQ: I did studies on prophylactic treatment with phenothiazines in schizophrenia. I probably had 30 publications before I went to Columbia, perhaps 40. I had a wonderful close collaboration at Hillside with Arthur Rifkin.

TB: Could you elaborate on your findings on prophylactic treatment with phenothiazines in schizophrenia?

FQ: The drugs made a big difference, which was the bottom line.

TB: What was your latest publication?

FQ: A paper in which I evaluated the work of Fisher and Greenberg when they say that double-blind studies are not double-blind because guesses exceed chance.

TB: You have been working with Don Klein your entire research career.

FQ: I am extremely fortunate to have worked with Don Klein. He was always fair and an inspirational model and we had very good support at Hillside. The medical director liked research. Being at the New York State Psychiatric Institute was a stroke of luck, because we didn't have to worry about soft money and were given a lot of options. So I deem myself blessed. I try not to depend too much on drug companies, and to keep opportunities for my intellectual curiosity.

TB: Is there any particular drug you found more interesting than the others?

FQ: I don't think that there are differences between the drugs produced in 1958 and the new ones. The new ones are more user-friendly but, in terms of efficacy, I don't think one is better than another. The main difference with antidepressants is how people tolerate them, which is unpredictable. They are approximately equally effective, although there is an advantage in atypical depression with MAO inhibitors. However, MAOIs are no longer first-line drugs.

TB: In addition to many papers, didn't you publish a book?

FQ: I wrote a book with Don Klein, Rachelle Klein, and Arthur Rifkin. It was a lot of work, but I learned a lot.

TB: At the time you entered the field, there were very few psychotropic drugs available, primarily phenothiazines.

FQ: You are right. When I started, around 1963, there were only a very few psychotropic drugs. We've made enormous progress.

TB: Would you like to talk about people you worked with?

FQ: I have been extremely fortunate in that I've always worked with people I had collegial relationships with. First, I worked with Arthur Rifkin and John Kane, with whom I still have a good relationship. When I went to Columbia, I began working with Jonathan Stewart, Pat McGrath, and Ned Nunes. I've had relationships with colleagues who I trust, who're very bright, and hard working. A lot of things fell into place. I view myself as extremely fortunate in that respect.

TB: Is there anything else you would like to mention?

FQ: We hit on most of the things. It's been a lot of fun. I wouldn't mind doing it for another 40 years.

TB: Are you still fully active?

FQ: Absolutely. The best is yet to come!

TB: That's very good. Well, thank you very much, Fred.

FQ: Thank you.

54. ELLIOTT RICHELSON

TB: We are at the annual meeting of the American College of Neuropsychopharmacology in Hawaii. It is December 9, 2001, and I will be interviewing Dr. Elliott Richelson⁵⁶ for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Elliott, tell us where and when you were born, about your early interests and education, and how you got involved in neuropsychopharmacology.

ER: I was born in Cambridge, Massachusetts on April 3, 1943 and raised in a town close by called Waltham. My father was a dentist and my mother a secretary. I went to public schools in Waltham. In high school, I had a chemistry teacher who was very influential in getting me interested in science, so I majored in chemistry at Brandeis University in my hometown. But even before then, in high school or earlier, I had interests in becoming a physician with the idealism of youth, to help people. I didn't want to be a dentist because I saw what my father did and that didn't interest me. I also thought in college that the best way to help a lot of people is to do medical research, because a physician can only see so many people in a lifetime, but if you develop a treatment for a disease, you could help millions potentially. Those were the things I was thinking about in college. I did have some interest in psychology, took a course or two and did some reading on Freud in high school and college. I went to the Johns Hopkins University School of Medicine where it was required, as part of the pharmacology course, to write a thesis supervised by one of the faculty members in the department.

TB: Was this in the early 1960s?

ER: I graduated from Brandeis in June of 1965 and started at Hopkins in the same year. Sol Snyder was a new faculty member in the Department of Pharmacology and it was from his influence I am in psychopharmacology; he was my mentor for the thesis I had to do. We worked on a project together; it was armchair chemistry in which we related the structure of some psychedelic drugs

⁵⁶ Elliott Richelson was born in Cambridge, Massachusetts in 1943. He received his M.D. from Johns Hopkins University School of Medicine. After an internship in straight medicine at Washington University in St. Louis, he went to NIH to the laboratory of Dr. Marshall Nirenberg for post-doctoral training. He completed his residency in psychiatry at Johns Hopkins, while on the faculty of the Department of Pharmacology. He was then recruited to join the faculty of the Department of Psychiatry at the Mayo Clinic, where he has worked in Rochester, Minnesota, and more recently, at Jacksonville, Florida. He was interviewed in Waikoloa Village, Hawaii on December 9, 2001.

to serotonin. From that came a paper we published in *PNAS*. The paper is probably of no import, the importance was contact with Sol Snyder.

TB: Was it your first paper?

ER: It was not my first paper.

TB: Did you do any research before?

ER: From early on in college, I started to do research. My first research job was the summer after my freshman year, when I worked at a Dow Chemical facility close to my hometown doing synthetic organic chemistry.

TB: What was your first paper?

ER: I did a senior honors thesis in chemistry as part of my undergraduate work and that led me into the Biochemistry Department. Nathan Kaplan was Chair and I co-authored a paper with Mary Ellen Jones, my supervisor.

TB: What about in medical school?

ER: I was involved with two research projects, one with Sol Snyder I already mentioned and another one with Dan Nathans who won the Nobel Prize, along with Hamilton Smith and Dr. Werner Arber from Switzerland, in 1978. I spent a full 12 months while in medical school in the laboratory of Dan Nathans.

TB: What was your project with Dan Nathans?

ER: I was working on RNA bacteriophages and looking at protein RNA interactions. It was very exciting, although I didn't appreciate it fully at the time.

TB: Even if you did not fully appreciate it, it had to be a very stimulating environment.

ER: In the adjacent laboratory to Dan Nathans, Hamilton Smith was trying to infect a haemophilus bacterium with a bacteriophage and the bacteria were resisting the infection. He just could not succeed but ultimately recognized the bacterium had an enzyme which cleaved the DNA of the injected bacteriophage; that led to the discovery of restriction endonucleases.

TB: This took place in Hamilton Smith's adjacent lab?

ER: Yes, but Dan Nathans used those enzymes to selectively and precisely cut up DNA, working with a virus called SV40, simian virus 40, to figure out what the various genes were doing. The discovery of the first restriction endonucleases led to where we are today in the human genome

project and genetic engineering. So, I was associated with that project and very fortunate to have interactions with such incredibly intelligent folks like Dan Nathans and Sol Snyder.

TB: So you were involved in two research projects while in medical school.

ER: Also, somewhere early in medical school, I went back to Boston and did a summer at Mass General working on a thyroid biochemistry project, which, unfortunately, didn't go anywhere.

TB: How did you get involved in psychiatry?

ER: This happened later. When I entered medical school, Joel Elkes was Chair of Psychiatry, and Paul Tallalay was Chair of Pharmacology. But very shortly after arriving at Hopkins, Dr. Elkes and Dr. Tallalay both resigned, so things were in flux. But I did enjoy my interactions with Dr. Elkes and still value him as a colleague and friend. I was interested in psychiatry, but ambivalent about making that my clinical specialty. It was either neurology or psychiatry, but I postponed the decision for a while. My association with Dan Nathans led me to apply for a research fellowship at NIH, after my internship year.

TB: Where did you do your internship?

ER: I did my internship in straight medicine at Washington University in St. Louis and then went to NIH to the laboratory of Dr. Marshall Nirenberg. Marshall Nirenberg had won the Nobel Prize two years before I joined his laboratory, in 1970, for working out the genetic code. He shared that prize with a few others.

TB: The second Nobel Laureate you worked with.

ER: Right. It's interesting how things evolve because when I interviewed at NIH for a position, my first choice was not Marshall Nirenberg. I hope he doesn't see this tape. It was to work in Dr. Kaufman's laboratory. He was an outstanding scientist, an enzymologist, who purified and isolated phenylalanine hydroxylase; he was involved with tyrosine hydroxylase as well. I didn't get my first choice and went to Marshall Nirenberg's laboratory instead, which was great luck. My stay in his laboratory was a marvelous experience, trying to soak up as much knowledge as I could. Because of his stature, he attracted outstanding young scientists to his group, who were a lot more sophisticated and knowledgeable than I in biochemistry and molecular biology. One of them was Al Gilman. Marshall Nirenberg liked to have definite ideas about who should be working on what in his laboratory, but Al Gilman managed to work on a project that he was interested in. This project involved β -adrenergic stimulation of cyclic AMP production. And it was seven years ago,

in 1994, that Al Gilman shared the Nobel Prize for the work he started in Marshall Nirenberg's laboratory, in about 1970. Those were probably the best two years of my career in terms of setting me up for future research, because of the knowledge I gained in that environment. NIH was a superb place to be; I worked very hard and learned a heck of a lot. About a year and a half, maybe less, into that fellowship, Sol Snyder paid me a visit. He wanted me to come back to Johns Hopkins to join his division of psychopharmacology and to work it out, so I could also do my residency in psychiatry. You call this, "Doing the Sol Snyder," because that's what he did. When I was a medical student at Johns Hopkins and Sol was an Assistant Professor of Pharmacology, he was also a resident in psychiatry, so that's what I did. I returned to Johns Hopkins as an Assistant Professor of pharmacology and a resident in psychiatry; this was a great way to do psychiatry because I'd be able to have some sanity in my life by working in the laboratory. So I got my first NIH grant, while doing my training in psychiatry. It was towards the end of my residency, when Dr. Tallalay was resigning and Dr. Elkes had already resigned, that I made a presentation in Montreal, at the meeting of the American Society for Pharmacology and Experimental Therapeutics.

TB: When was that?

ER: The summer of 1974. There were a couple of folks at the meeting from Mayo, one of whom was Richard Weinshilbom. An absolutely brilliant man I had met at NIH, when he worked with Julie Axelrod on dopamine β -hydroxylase in the blood. He had gone to Mayo a couple of years before and was on a search committee to find a biologically oriented psychiatrist; so he asked if I would be interested. I was, so I went to Rochester, Minnesota in November 1974. It was a lot colder in Rochester than Baltimore but I was very, very impressed with Mayo. They made an offer I couldn't refuse and 26 years later I'm still there, except, 12 years ago, Mayo again made me an offer I couldn't refuse; to transfer to Florida. After spending 14 winters in Minnesota, I was happy to take the job!

TB: When did you start at Mayo?

ER: I joined the Mayo Clinic on July 1, 1975 and held a primary appointment in the Department of Psychiatry with a secondary appointment in pharmacology. My office and laboratory were in the Guggenheim Building, across from the Mayo Clinic building. I spent one afternoon a week seeing patients, which I still do after 26 years. That has given me firsthand experience with the

drugs we study in the laboratory. The Mayo Clinic is very different from a university; you can be on staff and not have an academic appointment. In universities, the medical school comes first and the hospital is built around the medical school; Mayo Clinic was a clinic for almost 100 years before they decided to start a medical school. The Mayo Clinic in Rochester has two separate hospitals, and in the early 1970s, they decided to start a medical school; my recruitment was related to beefing up the staff for that purpose. But, as I said before, one can have an appointment at Mayo Clinic but no academic appointment. We're called Consultants at the Mayo Clinic. I'm a Consultant in Psychiatry and Pharmacology at the Medical Center, but I'm also a Professor of Psychiatry and Pharmacology at the Mayo Medical School and at the Mayo Graduate School for Medical Education. There is a story why we are called consultants at the medical center.

TB: What is the story?

ER: The Mayo brothers, who started the first group practice in medicine at the end of the 19th century that grew into the Clinic, were both surgeons and they brought on staff internists to consult if they thought the patient had a medical problem. So in this first group practice of medicine they established, they called their staff consultants.

TB: I see.

ER: The Mayo Clinic is one of the world's great medical institutions, but the Mayo Clinic is not doing much in the way of research. So, my Career Development Award from NIH, which I obtained at Hopkins, could not be transferred to Mayo. Nonetheless, I continued my research and flourished, published a lot of papers and accomplished things.

TB: What was your first research project after you arrived in Rochester?

ER: It was a continuation of what I was doing at Johns Hopkins, studying the regulation of tyrosine hydroxylase.

TB: Could you give us the background to that project?

ER: When I was at NIH in Marshall Nirenberg's laboratory, he was interested in developing model systems of neurons that grow in culture, so he could study the chemistry of neuronal cells, What he wanted to develop in culture was synaptogenesis, and he succeeded. My project was to isolate a cell line with high levels of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines. He had been working before I got there on an established cell line of a tumor that was a neuroblastoma, from the mouse. The neuroblastoma was a spontaneous tumor serially

transferred from mouse to mouse for many years until, in the early or mid-1960s, somebody took the tumor from an animal, dissociated it, and grew it in culture. Those cells were called mouse neuroblastoma C1300, made up of many different cell types. Now we think about neuroblastomas as being adrenergic tumors, but we had difficulty even measuring tyrosine hydroxylase activity in those cells.

TB: What was your task in that project?

ER: My task was twofold. First, I was to develop the enzyme assay for tyrosine hydroxylase; and folks had been trying to do this for a while before I came to Marshall Nirenberg's laboratory. It was very difficult to develop that assay because of the presence of inhibitors of this enzyme's activity in the neuroblastoma cells. In addition, the activity of the enzyme was very low. After I got the assay developed and working very well, we set about to clone it, to isolate a single cell from this heterogeneous population of cells. We used the glass shard technique. You place small broken pieces of sterile glass on a culture plate and then plate out cells at very low densities so you find either no cells or just one cell on a shard. Under sterile conditions, with forceps under a microscope, you pick up the shard with one cell and place it onto its own culture plate. If cells grow you're reasonably certain the population came from that single cell. We use the term cloning to mean other things now, but back then it was just cloning of cells. We had a very large number of cell lines I screened for tyrosine hydroxylase activity and found one cell line, N1E115 with exceedingly high, higher than the adrenal medulla, level of activity. This cell line is the most widely studied neuroblastoma cell line in the world. There are literally hundreds upon hundreds of papers published using this cell line. If the authors ever cited the original paper I'd have a certain citation classic, but nobody does!

TB: Where and when was it published?

ER: The Amano, Richelson, Nirenberg paper on "Neurotransmitter Synthesis by Neuroblastoma Clones," was published in *Proceedings of the National Academy of Sciences USA*, in 1972. So, when I went to Hopkins, I continued working with that cell line, studying the regulation of tyrosine hydroxylase because of its relevance to the action of some psychiatric drugs. Catecholamines have been important in theories of the pathophysiology of affective illness and the action of antidepressant drugs. At Mayo, I continued with that same cell line to study tyrosine hydroxylase, but then I became interested in its receptors.

TB: How did that come about?

ER: At Hopkins, from about 1973 to 1975, there was a scientist named Pedro Cuatrecasas, in the Department of Pharmacology. He was a brilliant man and brilliant researcher, who had developed radioligand binding assays and was interested in hormone receptors and particularly the insulin receptor. He taught Sol Snyder how to do binding assays, and Sol Snyder ran with the technology. I, quite frankly, was intimidated by all that receptorology going on at Hopkins and I did not move into the area until I went to Mayo. Then, I discovered that the cell line I studied, had muscarinic receptors, which, when activated, elevate intracellular levels of cyclic GMP (cGMP). With this functional assay measuring cGMP production in living cells, I was able to study muscarinic receptors in various ways, looking at agonist stimulation of the receptor, regulation of sensitivity of the receptor to various agonists and at desensitization and down regulation. I also used the assay as a way of looking at the potency of psychiatric drugs to block the muscarinic receptor. So we did studies determining inhibitor constants for antidepressants, antipsychotics, and related compounds by their ability to block receptor-mediated cGMP production. I wrote a paper with Divinetz-Romero, on the "Blockade by Psychotropic Drugs of the Muscarinic Acetylcholine Receptors" that won an A. E. Bennett Award from the Society of Biological Psychiatry, in 1977, and was published in *Biological Psychiatry* the same year. So we got into receptors in a big way. We also started to see if we could get any response from these cells by adding other neurotransmitters and discovered histamine worked quite well. We now had another receptor we could study by this functional assay, the histamine-H₁ receptor. Then we looked at the ability of antidepressants and other psychiatric drugs to block histamine-mediated cGMP production in these cells. From this work, we discovered drugs like doxepin were incredibly potent antihistamines. Next, we were interested to see whether peptides, particularly neuropeptides, had any effects on cGMP production in these cells, so we screened bradykinin, angiotensin, and neurotensin with this same cell line, N1E-115. We found, in the early 1980s, stimulation of cGMP by each of these peptides. The medical literature at the time was interested only in one of those peptides, neurotensin. In 1980, Charlie Nemeroff had published his A. E. Bennett Award paper, "Neurotensin Per Chance Endogenous Neuroleptic?" in *Biological Psychiatry*. Having discovered the neurotensin receptor on these cells and knowing this might be important in terms of a

psychiatric illness, we decided to focus on neurotensin and its receptors. To this day, we continue this research.

TB: So, you became involved in research with neurotensin?

ER: We have a patent issued last April, U.S. Patent No. 6,214,790, on some of the neurotensin analogs we have, and we're moving forward with preclinical toxicology studies to get one of these compounds into humans and see if it has any antipsychotic effect. Now, what goes around comes around. There's evidence neurotensin has to be directly injected into the brain to get an effect, but our neurotensin receptor agonists can be injected outside the brain and still get into it. There's also literature to suggest neurotensin can activate and up-regulate tyrosine hydroxylase.

TB: So you are back to tyrosine hydroxylase?

ER: I'm back where I started. It's incredible! I'm doing experiments we did 30 years ago. So, we thawed out the N1E-115 cells, we're growing them and looking at the ability of neurotensin to inactivate tyrosine hydroxylase. We want to understand the basic mechanisms involved.

TB: You mentioned you have a model for studying receptor binding for acetylcholine, histamine, and neurotensin, right?

ER: Yes.

TB: And you have published on receptor binding with different series of psychotropic drugs?

ER: Yes, thank you for reminding me. We had a wonderful neuropathologist at Mayo in Rochester, Dr. Okazaki, and when there was criticism about doing binding studies on rat brain or studies on receptors in mouse cells, it occurred to me maybe we should do human brain binding studies. So I went to Okazaki; he was incredibly cooperative and happy to provide us with normal human brain tissue whenever we needed it. He's co-author on a series of studies that looked at binding of psychotropic drugs to several different receptors in normal human brain tissue. We included studies on antipsychotic drugs and antidepressant drugs, defining their receptor binding properties at human brain receptors.

TB: You have delineated the receptor profile of numerous psychotropic drugs in humans?

ER: Exactly. We still have to do a few binding studies with human brain tissue, but with our capability for molecular cloning of human receptors, it's unnecessary to get the tissue at autopsy any longer. Nowadays it's almost impossible to get normal human brain tissue at autopsy. We have a brain bank at Mayo, in Jacksonville, with hundreds of brains from Alzheimer's,

Parkinson's, and other degenerative diseases, but normal brain tissue is very hard to come by. At the time, we were envied by many, because it was hard for colleagues to get the normal human brain tissue we had been able to obtain. So we were in the forefront with respect to that research. From the data we've obtained, we continue to fill in gaps by looking at new drugs when they become available. I've published many review articles on receptor binding of antidepressants and antipsychotics and what that relates to clinically, mainly side effects. I think I'm best known for these review articles rather than the many more basic science papers I've published.

TB: Your review articles are based on your own research?

ER: Correct. On findings we reported in peer reviewed basic science journals, such as *European Journal of Pharmacology*, *Journal of Pharmacology and Experimental Therapeutics*, etc. In my review papers, I interpreted the findings in those papers for clinicians.

TB: I have been using the data from your review articles as reference points for many years.

ER: Thank you.

TB: I don't think anyone had studied the receptor profile of antidepressants and antipsychotics as systematically as you.

ER: That's correct but I don't consider this terribly creative research. It is clinically very important for predicting adverse effects and making it possible for clinicians to choose a treatment on the basis of the receptor binding profile of a drug.

TB: You were first to provide information that should be available for any new drug.

ER: I think we're seeing this information now in new compounds.

TB: Drug companies are providing the information now.

ER: Yes, they are selecting compounds for clinical development with weak effects at least on muscarinic acetylcholine, α_1 -adrenergic, and histamine- H_1 receptors. What I provided was a standard with respect to one laboratory compiling the data and rank ordering the drugs.

TB: What kind of interaction do you have with drug companies?

ER: I have had small grants from pharmaceutical companies to look specifically at the receptor binding profile of their compound in human brain receptors compared to standard compounds. But it's been a minor effort in terms of overall production.

TB: Each company is doing this now in-house? Is each company doing it the same way?

ER: They're looking mainly at cloned human receptors. They don't have available the human brain tissue we still have.

TB: You still have?

ET: Yes. So occasionally a pharmaceutical company will come to me for the human brain receptor binding profile of their compound.

TB: What do we know about interspecies differences in receptor binding?

ER: There are clearly species differences but they are working with cloned human receptors. Still, because of potential artefacts introduced when you're looking at a molecularly cloned human receptor, actual human brain studies are worthwhile.

TB: You mentioned the work you are doing is relevant to adverse effects but does it have any relevance to the therapeutic effects, for example in neuroleptics? Do you think the affinity of neuroleptics to the dopamine-D₂ receptor has any relevance to the therapeutic effect?

ER: Certainly. In 1976, Snyder's group published with rat brain and Seeman's group with calf brain, some studies with a marvelous correlation between dopamine-D₂ receptor binding and daily dosage. We recently did the human brain and got the same results. For sure, the dopamineD₂ receptor is important in therapeutic, as well as adverse effects.

TB: Is it relevant to schizophrenia or to psychosis?

ER: It's a good question. It's amazing Snyder's and Seeman's groups both showed, from a test tube assay, that affinity to the dopamine-D₂ receptor on the Y-axis and daily dose on the X axis have a high correlation.

TB: But isn't that a relationship between dose requirement and receptor affinity?

ER: With PET (positron emission tomography) scanning, using radioligand binding assays, we can look at receptor occupancy for dopamine-D₂ receptors, serotonin receptors, and the like in vivo in humans and relate the findings to both therapeutic and adverse effects.

TB: Are the findings state dependent?

ER: Not really. That's important, but I'm of the mind we can't be certain about the mechanism of action of these drugs and I decided a long time ago I can more easily explain the mechanism of an adverse rather than a therapeutic effect.

TB: Do we have enough information, at this point, to generate a hypothesis regarding therapeutic effects?

ER: I think dopamine-D₂ receptor occupancy relates to therapeutic effects in psychosis and also extrapyramidal side effects, but I don't necessarily think that means an aberration of the dopamine system per se explains what psychosis is.

TB: You are always very careful in your papers, much more careful than other people, in relating your findings to therapeutic effect and disease.

ER: Thanks.

TB: What about serotonin receptors?

ER: There's a lot of controversy about serotonin 5HT_{2A} receptors. We found if you knockdown the gene for the 5HT_{2A} receptor you block haloperidol induced catalepsy.

TB: That is very interesting.

ER: So, the 5HT_{2A} receptor is very important in terms of modulating or ameliorating the adverse effects of neuroleptics.

TB: What about antidepressants?

ER: We've just determined, with Randy Blakely, the binding inhibitor constants in very large series of antidepressants and antipsychotic drugs for potency of binding to transporters; that information has been useful in predicting side effects but not efficacy in treating depression.

TB: By binding to transporters, reuptake is blocked, right?

ER: Correct.

TB: Again you are saying it has something to do with adverse effects, but is there a relationship between blockade and therapeutic effects?

ER: There may be but one should not overlook there are major differences in potency binding to norepinephrine and serotonin transporters of equally effective antidepressants. Moreover, we have drugs like trimipramine, which are not very potent at norepinephrine, serotonin or dopamine, yet are effective antidepressants.

TB: I remember early behavioral pharmacological findings with trimipramine which indicated it could be administered safely in combination with monoamine oxidase inhibitors.

ER: Of course.

TB: What about venlafaxine? Its effect on reuptake looks like the mirror image of imipramine.

ER: Venlafaxine is much more potent on the rat norepinephrine transporter than the human.

TB: So, the effect of venlafaxine is weak on the norepinephrine transporter in humans?

ER: In our hands, venlafaxine in the rat is about four to five times more potent at the serotonin transporter than at the norepinephrine transporter, whereas in humans there is a 100 fold difference.

TB: So we have to push the dose high to get any norepinephrine effect, otherwise it's like an SSRI?

ER: Yes, at low dose, it is an SSRI.

TB: You seem to be splitting your time between basic and clinical research?

ER: I continue to be interested in basic research, but now I'm trying to get drugs we've been working on in the laboratory into the clinic. The ultimate goal of the pharmacologist, and I look at myself as a pharmacologist, is to get a drug into the clinic. To do that in academia is extremely difficult, but we're moving in that direction. We have, as I mentioned, a patent for a neurotensin analog, and I've secured funding to do preclinical toxicology through a foundation, so I can get it into the clinic. If this compound passes preclinical toxicology, I should be able to get an IND for testing it in schizophrenic patients. That will test the hypothesis Charlie Nemeroff proposed 20 years ago, that a neurotensin agonist would be an antipsychotic. My goal, before I retire, is to get at least one of the compounds we've been working on for many years into the clinic and be involved personally in the clinical trial.

TB: The compound is a neurotensin agonist you would be testing in schizophrenia?

ER: Yes. But what is very interesting about this compound is that it might also be very useful in Parkinson's disease. We have data which suggest that, like some antipsychotic drugs, it blocks the behavioral effects of psycho-stimulants such as cocaine and amphetamines. So we have a unique compound that in animal studies suggests efficacy in both schizophrenia and Parkinson's disease, while our current antipsychotics induce parkinsonian symptoms in patients.

TB: It would be interesting to have a compound that is effective in both schizophrenia and Parkinson's disease. Do you have any other compound in the making?

ER: I'm co-inventor on a patent issued in May 1999 for a series of compounds that are analogs of venlafaxine. For some of these compounds, I use the acronym SNUB, because they are potent blockers of all three transporters; norepinephrine, serotonin and dopamine. These are compounds of a chemist I collaborated with at another institution.

TB: Are these the first SNUBs?

ER: Apparently there are pharmaceutical companies around the world that have these types of compounds in development. But these could be phenomenal antidepressants if you remember nomifensine.

TB: I remember nomifensine very well.

ER: We have a number of other patent applications pending on a whole other area of research I haven't mentioned.

TB: Would you like to say something about them?

ER: We have been involved for five years looking at a new generation of compounds, called peptide nucleic acids, PNA for short. That's a misnomer because they are neither peptides nor nucleic acids and they are not broken down by either peptidases or nucleases. We did studies with these types of molecules to answer questions about the neurotensin receptor. Nobody had ever done research with them, other than in vitro experiments with cells in culture. What researchers observed was they didn't penetrate well into cells. Nonetheless, we went forward with animal studies and were able to knock-down gene expression in brain by directly injecting these molecules into brain. The next experiment was to inject them into the belly of the rat and we showed an effect in the brain, as long as there was no impairment of the blood-brain barrier, which was quite revolutionary. This is the great thing about science; you have a hypothesis, do an experiment, and get a result which is unexpected. Then, you continue down a road you never thought you'd travel on.

TB: What would you consider your most important contribution?

ER: I'm not sure, quite frankly. I alluded to the fact I'm best known for my review articles. I'm proud of that because I've tried to take basic information and make it relevant and readable for the clinician; to bring the basic pharmacology of drugs we use every day to the level of clinicians, so they can understand and use it in clinical practice.

TB: You are still involved in clinical practice?

ER: Once a week, half a day, all through the years.

TB: Do you see any patient or just a selected population?

ER: Good question, I see two patients in consultation weekly. The Mayo Clinic, in Jacksonville, has about 300 physicians now. It opened, in 1986, with less than 40. It's a multispecialty clinic. The patient comes in for a medical work-up and if a colleague thinks a patient has a psychiatric

problem, they receive a psychiatric evaluation. I set aside a couple of slots in my afternoon schedule to see whatever, it can be anything.

TB: They are patients from the Mayo Clinic?

ER: Generally. But then I have a group of patients I've been following for years. They are the most difficult, refractory, depressed patients you'd ever want to treat, which keeps me honest and running back to the laboratory to develop better drugs. I do a lot of experimentation with them which they understand and accept.

TB: When you say experimentation are you following an intensive study design?

ER: I'm not doing anything as systematic as that. I'm trying many different things, combining drugs, using drugs not necessarily considered first line treatment, or not even indicated for the condition.

TB: Could you say something about your training in psychiatry at Hopkins?

ER: Psychiatric training at Hopkins at that time was very analytically oriented.

TB: After Joel Elkes resigned?

ER: Even when he was there. So I had to do a lot of psychotherapy and didn't particularly like that. I wasn't good at it. You don't have to be a physician, or even a college graduate, to do psychotherapy. I may offend folks by saying it's a waste of a time in medical schools, training someone to be a psychotherapist. A psychiatrist is first a physician and should not renounce the knowledge gained in medical school, as some have done. That doesn't make sense. The way to remain a physician, while being a psychiatrist, is to practice pharmacology. To practice psychiatry well and treat people with drugs, you have to know a lot about your patient's health and need to be knowledgeable about internal medicine.

TB: When did you become a member of ACNP?

ER: When I went back to Hopkins to work with Sol Snyder, who got me invited to ACNP.

TB: What year was that?

ER: Around 1972. and I never missed any of the annual meetings. I became a member, in 1976. I was also involved in the Society of Biological Psychiatry. I don't know if I should talk about that.

TB: Please do.

ER: I was Secretary/Treasurer for five or six years, then became Vice President and President, and now I continue to be on the Council. I have been so active with the Society of Biological Psychiatry, I may have neglected the ACNP, but I'm now the incoming Chair of the Credentials Committee.

TB: You mentioned you received the Bennett Award of the Society of Biological Psychiatry.

ER: Yes.

TB: Any other awards you have received?

ER: The Daniel Efron Award of the ACNP, which I shared with Bob Post. That was quite an honor.

TB: What is your position now at the Mayo in Jacksonville?

ER: I'm the first Director of Research. I started research from scratch, which was enormously difficult, but I had a lot of help. If you can imagine working in trailers for four years, before we had a building! We started from a site, where we didn't even have permission from the state to use radioactive materials; we had to go through the process of filling out applications and applying to the State just to do the first experiment with radioactivity. It was starting from scratch and quite difficult for seven or eight years. The focus of research in Jacksonville was on Alzheimer's and neurodegenerative diseases, which made my situation even more difficult because I didn't consider myself an Alzheimer's researcher. But, I had enough interest in the field and liked the idea of going to Jacksonville so much, I jumped at the job. The second Director for Research is a very distinguished scientist in the Alzheimer's field, Steven Younkin. He, in turn, recruited some outstanding researchers and we have made our place a first-class research institute in Alzheimer's and other neurodegenerative diseases. So that's going well.

TB: Is there anything we left out and you would like to add?

ER: I'm impressed with how much you know about what I've done and I appreciate that.

TB: You've done a great job, in addition to your other research, by translating findings from basic science to clinicians. You certainly achieved your objective and should be happy about that.

ER: Thank you.

TB: I would like to wish you good luck in developing the compounds generated through your research.

ER: Thank you very much.

TB: Thank you, Elliott, for sharing this information with us.

ER: My pleasure. It was fun.

55. ALAN F. SCHATZBERG

TB: This will be an interview with Dr. Alan Schatzberg⁵⁷ for the Archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the College in Waikoloa, Hawaii. It is December 12, 2001. I am Thomas Ban. Let us start from the very beginning. Tell us where and when you were born, something about your early interests, education and professional training?

AS: I was born in Manhattan in New York City, in October 1944. My parents immigrated to the United States in January 1940, after the onset of the war in Europe. They came from Vienna. My father went to Vienna, in 1914, from Galicia, and my mother went there in 1922, to be a college student. She met my father and they got married. My father was a 1925 graduate of the University of Vienna Medical School. His two brothers were also graduates. My father was a dentist in Europe. Because of anti-Semitism many Jewish doctors became dentists. Dentistry in Vienna and in many European countries was a sub-specialty of medicine. When my father came to the States, he became a general practitioner, practicing in the Bronx. I have an older sister who was born, in 1934, who is a psychiatrist in New York City. She trained at Columbia. So, medicine is an important profession in the family.

TB: Were your grandparents also in medicine?

AS: No. My grandfather on my father's side managed a wheat mill and my grandfather on my mother's side was a successful businessman in Galicia, in the lumber and leather tanning business, the kind of occupations that European Jews participated in. They were upper middleclass folks who left after the onslaught in Vienna. I was born in the States, but my sister was born in Vienna. So I grew up in the Bronx, went to Bronx High School of Science, and after three years, to college, then on to medical school at NYU. At that point, they had an uptown campus in the Bronx. After graduating, I did my internship in pediatrics and medicine. For residency, I went to Mass Mental Health Center, the main Harvard Medical School psychiatric teaching program, and was there

⁵⁷ Alan F. Schatzberg was born in Manhattan, New York in 1944. He obtained the M.D. degree from New York University School of Medicine in New York, New York and trained in psychiatry at the Massachusetts Mental Health Center in Boston, Massachusetts. After serving in the Air Force, he returned to Boston to join the faculty of Harvard Medical School at McLean Hospital in Belmont, Massachusetts. He eventually joined the Massachusetts Mental Health Center and then went to the Stanford University School of Medicine, in Stanford, California. He was interviewed in Waikoloa, Hawaii on December 12, 2001.

from 1969 to 1972. At Mass Mental, I met Joe Schildkraut and that was important in terms of my career. From 1972 to 1974, I served in the US Air Force during the Vietnam War, stationed at the Pentagon, helping the Air Force set up drug and alcohol abuse programs and also with programs in race relations. They were very forward thinking, trying to deal with racial integration in the US Air Force. After two year, in 1974, I went back to Harvard and was recruited by Shervert Frazier at McLean Hospital to set up a depression research program with Joe Schildkraut, who was still at Mass Mental Health Center. He was the catecholamine hypothesis person. I was also scheduled to work with Harvey Schein, a virologist and psychoanalyst, who was the clinical director at Mass Mental Health Center and professor at Harvard, but who tragically passed away at a relatively early age before I arrived. Shortly after I got there, Jonathan Cole moved from Boston State to McLean. Jonathan and I became coresearch partners, collaborative colleagues and friends. So I had these two very important people in American psychiatry as mentors; they got me interested in depression research, and so that's how it started.

TB: What was your first research project? Was it a project with Joe?

AS: My first publication was a single author paper; today these are rare, but it was on the trial and appeal of Wilhelm Reich, published in the *Archives of General Psychiatry*. Mass Mental was a very rich place intellectually and a fun place to be. In learning about psychoanalytic theory at the time, I came across some stuff about Wilhelm Reich and, having grown up in New York, I knew a little bit about what happened to him. It was a tragic story; he died in prison.

TB: Would you like to tell us more about your paper?

AS: I went to the U.S. courthouse and got hold of transcripts of Reich's trial and appeal. This is particularly interesting because Reich was quite paranoid and fired his lawyer. His original lawyer was James D. St. Clair who represented Richard Nixon in Watergate. Reich represented himself and wrote his appeal that has become a rich source for seeing his paranoia. Danny Friedman liked the paper and published it. Before I got into depression research, I also did some work in sexual behavior with Lee Burke at Mass Mental Health Center and in the psychological aspects of drug abuse, publishing papers with Ed Khantzian and John Mack, who were at Cambridge. When I got back from the Air Force, I started work with Joe and Jonathan on catecholamine turnover and responses to norepinephrine uptake inhibitor drugs. Joe was very interested in MHPG, and data

which indicated that people with low catecholamine turnover seemed to be responsive to norepinephrine uptake inhibitors.

TB: Am I correct that you have continued that research and just a couple of years ago still published on MHPG and drug response.

AS: We have. We looked at catecholamines as differential predictors to desipramine and nortriptyline, tricyclic drugs we did a lot of work with, and fluoxetine, an SSRI. We predicted that people with high average MHPG levels would be SSRI responsive but what we found was that the people with low MHPG levels were generally responsive to all those drugs. So that led to further confusion in the field. We also did a fair amount of research with Joe, looking at so-called “computer algorithms of catecholamines” and catecholamine metabolite excretion. We were developing D-type equations which looked pretty good at separating bipolar I depressives from unipolar nonendogenous depressives. We were one of the first groups to show a linear correlation between the excretion of urinary MHPG and urinary cortisol; that finding has been replicated several times, looking at plasma, CSF, and whatever. A paper last year in *PNAS* showed that norepinephrine and CRH go together. So this high output state, described by us in 1983, has been replicated and that’s nice. At the same time, because we were looking at MHPG as a predictor of response to antidepressants, we became very interested in lots of issues about depression and especially refractory depression. Why are some patients non-responsive to antidepressants or they don’t tolerate the antidepressants? Sometimes they don’t take enough, either because the physician doesn’t prescribe it or because they can’t tolerate it. So, we became very interested in how to define treatment resistant depression. This is another place that you did a tremendous amount of work in 20 years ago, as did a number of people. We organized, in the mid-1970s, a symposium at the APA on treatment resistant depression in Atlanta. It was John Davis, myself, Sandy Glassman, Jon Cole and I forget who else. We were hoping we’d get 100 people to attend, and when I walked into the room, there were 700 people there because this was a common clinical problem. So depression has always been our big interest and we’ve continued to do work in that area.

TB: Could you say something about your two “mentors,” Joe Schildkraut and Jon Cole?

AS: Well, they are diametrically opposite personalities. Joe is compulsive, careful, methodical, nitpicky, doing it in his own way, an incredibly good scientist, but at the same time, what people

don't realize about Joe, enormously creative. He has a tremendous vision and is a very interesting person. He is also one of the great experts in the world on Joan Miro and when the Guggenheim did a retrospective on Miro, about six or eight years ago, they had five citations, one of which was Joe Schildkraut's paper. And Joe also authored a book that is a compendium of presentations called *Homage to Miro*, published by Abrams. It's a terrific book based on a symposium he organized with Nancy Andreason at the Miro Foundation. He has also written some wonderful papers about the New York Expressionists School, including Jackson Pollack, Gorky, and others; so he is a real renaissance man and a genius. Jonathan is a totally different person, lovable with an infectious personality, charming, witty, and generous to a fault, somebody who does not care about appearances. He has made tremendous contributions to psychopharmacology as one of the first Presidents of the ACNP and Director of the Psychopharmacology Service Center. I was fortunate to have both of them as mentors, even though each could drive you crazy in different ways.

TB: What was your first project with Jon?

AS: I think our first paper looked at tricyclic side effects. We did a paper on speech blockage, word finding problems that people on tricyclics have. We described a series of cases and what to do about them. We published an interesting paper in *Archives* on preventing seizures due to maprotiline, which is a drug you were heavily involved in developing. We had about 14 seizures at McLean, so we were able to document that the seizure was due to dose escalation. We also showed what the plasma level threshold was for seizures and worked with Ciba-Geigy to change the package insert to recommend a 75 mg initiation dose for two or three weeks before increasing to the maximum dose, with a rollback after six weeks. We did a paper on trazodone in refractory depression and a study on thioridazine in borderline personality. Jon was very helpful to our group when we got interested in the question of psychotic or delusional depression and we came out with our first hypothesis paper, in 1985; he was one of the authors with Tony Rothschild, Phil Langley and Ted Bird, director of the brain bank at McLean. Jon and I, in 1975, started an affective disease program that may have been the first specialty mood disorders program. We remained co-directors until I left McLean, in the late 1980's, and our first resident was Bruce Cohen, now the general director at McLean, and a very well-known geneticist in bipolar disorder. Jon was an incredible mentor to young people and he, more than I, helped to train a number of terrific people, Sue

McElroy, Paul Keck, Steve Hyman, Bruce Cohen, and Trey Sutherland, who was at the NIMH. Tony Rothschild came through the mood disorders program, and Jon's enthusiasm and help was a boon to these folks. We taught them psychopharmacology.

TB: You wrote a book with Jon.

AS: In 1986, we came out with our *Manual of Clinical Psychopharmacology*. The American Psychiatric Press asked if we would do a book on psychopharmacology. Jon decided we would, if we could make it a non-exhaustive reference, because there were other books, like the Kline-Davis book, which summarized the evidence base but weren't so useful for practitioners. There were things we agreed with in the literature, and other things that didn't make much sense, so we wrote a book where we talked about how we practice, and which gave people tips. We are now completing the 4th edition of that book. The first three editions sold about 70,000 copies, so it has been a tremendous success in the field, and Jon and I remain co-authors. We've added a third co-author because of our schedules; a young faculty person at Stanford, Charles DeBattista. It has been great fun and it also has some humor in it. You can actually read the book; it is spiral bound, and it's done very well.

TB: Was it translated into any other language?

AS: Into Portuguese for Brazil and maybe into Italian. A lot of practitioners use the book around the world.

TB: Could you say something about the drugs you studied in your affective disorder program?

AS: We studied them all, including trazodone, maprotiline, bupropion and fluoxetine. Jon was very involved with bupropion development.

TB: In the 1980s, when the shift to SSRI's came, were you very involved with their clinical development?

AS: We were. Jonathan did one of the trials of fluoxetine, in the mid-1980s, and it was released in January of 1988.

TB: So, the affective disorder program at McLean Hospital was involved in clinical studies with new drugs?

AS: McLean Hospital was a very exciting place with a wonderful faculty. A person who was very important in my life was Shervert Frazier, Chief of Psychiatry. He was a visionary person who brought in many talented people. There was Evelyn Stone, a consulting editor for American

Psychiatric Press, who was interested in education. In 1977, at the American Psychiatric Association meeting, in Toronto, Shervert, Evelyn, Jonathan, and I organized a McLean symposium on benzodiazepines that included Don Klein and Dave Greenblatt. We had Wyeth as sponsor and it was a great success. There were 800 people in the room on a Sunday afternoon, before the meeting started. This was such a success, so every year, from 1977 on, McLean Hospital would have a symposium at the annual APA meetings.

TB: Didn't you write a paper on the overuse of benzos in depression around that time?

AS: We did. I was involved with Jonathan with benzos in two or three different areas. He obviously had a very strong interest in them as anxiolytics, but he also had a very strong interest in benzos because of their abuse liability. So he had developed a model for studying that. At the time, I had an interest in alprazolam as a potential antidepressant, so we did do some studies with alprazolam to test that. So, I became interested in the whole question of overuse of benzodiazepines in depression and the question of diagnosis; we published a paper, in 1978, in the *Archives* about that.

TB: McLean Hospital organized a symposium annually at the APA meeting?

AS: From 1983 to 1986. While Sherv Frazier was Director of the NIMH, I became the acting interim Psychiatrist in Chief at McLean. Since we had done studies with fluoxetine, we thought, in 1985, we should do an APA symposium on serotonin because fluoxetine and several other drugs were being developed that had effects on serotonin re-uptake. We organized a symposium for Sunday morning at the APA and fifteen hundred people showed up. The place was packed. The Lilly people, in the back, just couldn't believe it! Their projection for fluoxetine sales for a year or two was only about \$100 million. By the time the drug went off patent, in the U.S. alone, sales were about \$2.5 billion. We had our symposium two or three years before fluoxetine came out on the U.S. market. So we worked with some very successful drugs like fluoxetine, but we also worked with other drugs that didn't make it. Oxaprotiline was one that didn't make it and adinazolam was another. A lot of the drugs didn't make it for toxicity or other reasons.

TB: We keep on referring to McLean Hospital. Could you tell us something about its history?

AS: McLean Hospital was founded, in 1811 or 1812, as part of Mass General. Originally, it was in Charlestown, Massachusetts, where the Bunker Hill monument is and across the river from downtown Boston. McLean moved, in the late 1800's, to Belmont, Massachusetts to a campus of

a couple of hundred acres and multiple buildings, where people with disorders like Alzheimer's or dementia praecox could be hospitalized. There was no insurance in those days, so they were from families with wealth and a number of very famous people were hospitalized there. Alfred Stanton was Psychiatrist-in-Chief in the early 1970s and had an interest in the psychotherapy of schizophrenia. He was a well-known psychoanalyst, in Washington, D.C., before being recruited. In 1972, Sherv Frazier went there and started to recruit people. He recruited John Gunderson to work with Al Stanton; Jonathan Cole and myself, in depression work, as well as Seymour Kety, Ross Baldessarini, and Joe Lipinsky from Mass General. He set up a bipolar and schizophrenia program. Then, eventually he recruited Phil Holtzman, Steve Matthysse; Jack Mendleson, Nancy Mello, Roger Meyer, and Steve Mirin for drug abuse with Ed Shapiro for family therapy. He recruited outstanding people and built the Mailman Research Center, an unbelievably vibrant place. The transformation of McLean began in 1972; I went there in 1974; Jon joined at the end of 1974; Kety came in 1975. And as I told you, when he went to NIMH, I took over for two years. After he came back, I stayed, and from 1986 to 1988, I was running a large service and was an Associate Professor at Harvard Medical School. Then, in 1988, Miles Shore, the Director of the Massachusetts Mental Health Center, recruited me to become the Clinical Director and a full Professor at Harvard. I moved, in 1988, but kept my research group at McLean. I also had my private practice there. The Massachusetts Mental Health Center was a very different place. It was a state hospital basically; Joe Schildkraut was still there with his lab but was totally dependent on my clinical operation to produce the subjects for our research at McLean. So Joe wasn't doing much research at Mass Mental itself. Mass Mental got some money from the state, and when I moved over, I began to transform it into a kind of "intramural" research operation. Alan Greene had been an extremely productive researcher with atypical antipsychotics and Carl Salzman was doing work in geriatrics. So, we were able to start doing research at Mass Mental Health Center, while I was there from 1988 to 1991. After I left, Miles retired as superintendent, and went to the Harvard School of Public Administration. But research in schizophrenia continued with Alan Green, Bob McCarley, and others.

TB: When did you move to the West coast?

AS: In 1989, Stanford started recruiting me as Chair of Psychiatry, but there was a complicated arrangement, and so I eventually moved in August of 1991. I've been at Stanford as Norris

Professor and Chairman of the Department, since 1991, just over 10 years. For a while, I continued to do some research at McLean, although that petered out.

TB: What do you consider your most important contribution to the field?

AS: I think our current work on glucocorticoid dysregulation in psychotic depression is going to be extremely important. This work started at McLean with an observation that patients who were depressed and delusional, about 15 to 20 percent of depressed patients, have enormously up-regulated hypothalamic-pituitary-adrenal axis activity, with excessive production of glucocorticoids. We've been able to show they also have a very clear cognitive deficit, which involves the prefrontal cortex, probably the hippocampus and temporal lobe regions. We complemented these clinical findings with research in primates, in which we showed these regions are rich in low affinity glucocorticoid receptors, the so-called GR receptor, and that administering glucocorticoids to man or to primates produces cognitive problems very similar to psychotic depression. I recently reported with Joe Belanoff, (and we have another paper coming out based on a larger study), that mifepristone, which originated as RU-486, the French abortion pill, can rapidly improve psychosis in depression. We see 30 to 40 percent improvements in the BPRS scores in less than a week. The reason mifepristone works is that, while in low doses it is a progesterone antagonist, at high doses it is a potent antagonist for the low affinity glucocorticoid receptor in the frontal cortex and hippocampus, which is activated in periods of extreme stress. Since mifepristone has very little effect on Type 1 mineralocorticoid receptors, which mediate circadian rhythm and some other functions of glucocorticoid activity, we can block the bad part of cortisol release rapidly by using the antagonist. We're very excited about this work and are currently in Phase III with the studies. The development is by a company called Corcept I have been involved with. Organon is looking at a compound which has similar effects. This could be a very intriguing breakthrough for the field.

TB: And this project started with a clinical observation?

AS: Totally, from two clinical observations. One was that when we looked at 100 patients at McLean Hospital, we saw some patients with enormously elevated post-dexamethasone cortisol levels who were all delusional and psychotic. We then did studies looking at dexamethasone effect on dopamine metabolism by measuring homovanillic acid (HVA) and got some signals from there. We developed the idea this was not an epiphenomenon, the result of depression, but might be the

cause of some symptoms. Not necessarily the cause of the depression, but of cognitive problems in psychosis. So, it started from those observations. A lot of our work is funded by the NIMH. I'm particularly proud of this body of work we've been working on for almost 20 years.

TB: So, you already have some publications on this project?

AS: Jon Cole is on the paper we published in Joe Schildkraut's journal, the *Journal of Psychiatric Research* that Seymour Kety founded.

TB: You mentioned that besides mifepristone there is another compound in development with a similar action for the same population.

AS: Organon has a compound, but they are not studying it in psychotic depression because of certain intellectual property issues Stanford has.

TB: I see.

AS: I'm not totally convinced it's going to be a widely used drug because most depressed patients don't have increased glucocorticoid activity, but it will possibly be for the most severe, psychotic patients. We're particularly excited because this may be the first time we have a drug that starts with a clinical observation and ends up with a specific treatment. Tony Rothschild was supposed to present some of our recent findings today, but I will be presenting because he couldn't attend. Tony did an amazing study in which he took psychotic and non-psychotic depressed patients and controls and showed a nice relationship between cortisol activity and cognitive dysfunction. So this work has been totally exciting for us.

TB: It seems the population you are working with is biologically more homogeneous than other depressive populations in psychopharmacology.

AS: Yes. We have already contributed to an understanding of the biology of this population but if we can come up with a treatment that would be a terrific breakthrough.

TB: So, you consider your number one contribution to be glucocorticoid dysregulation in psychotic depression with cognitive deficit and its possible treatment. Any other exciting work you are doing?

AS: We are doing research in a squirrel monkey colony that Seymour Levine, a very well-known psychobiologist, retired from Stanford, put through a variety of early maternal-infant stressors. We reared six mothers and infants from this colony without the father. Then we looked at their responsiveness to stress at the point of weaning, at age three, and in early adulthood, as well as

their hippocampus size. We found that hippocampus size was not determined by early stress, but by whom the father was. So it's probably not so much that depression makes your hippocampus smaller, but that there are people with smaller hippocampus sizes prone to develop PTSD or depression. That's going to be an important paper in this month's *Archives of General Psychiatry*. It's going to be important, although controversial.

TB: Any other exciting projects?

AS: The third thing is recent work presented in a poster here. It is a study with mirtazapine versus paroxetine, done with a young faculty member of the department, Greer Murphy, a terrific geneticist, in which we've been able to show that a SNP of 5-HT₂ could predict dropouts on paroxetine. So we may have, for the first time, laboratory tests to predict which patients can tolerate SSRI's.

TB: Have you followed up your research on norepinephrine in depression?

AS: I did some research with Joe Schildkraut in that area. In the last few years, with the advent of drugs like venlafaxine, mirtazapine, and reboxetine, there is greater awareness of the role of norepinephrine in depression. The SSRI's, as a group, are great drugs for the mildly to moderately anxious and depressed person, but they may be lacking effectiveness in more severely depressed or retarded patients. When I started, what we called depression was different from what we call depression now. Nowadays, if you have four symptoms on the DSM, you make the diagnosis "major depression." We wouldn't have considered those people depressed in the old days. Back then, patients we called depressed were very impaired and many were near delusional or delusional. It's in that group I think norepinephrine plays a key role.

TB: Do you think there is a differential response for the more severe patients to norepinephrine re-uptake inhibitors?

AS: It's an interesting question. When you do meta-analysis, it's very hard to show the SSRIs are less effective. You talk, particularly to the Europeans, and they'll tell you that SSRIs are less effective in the more severely ill, and they have data to support that. They don't even use SSRIs in severe depression. If you look at data on reboxetine and some of the Italian data on reboxetine against fluoxetine, if you look at data on venlafaxine against fluoxetine, then norepinephrine reuptake inhibitor drugs or mixed uptake blockers do better in severe depression. If you look at FDA submissions, about half of inpatient studies have shown that venlafaxine and reboxetine

would be better than the SSRI and about half not. And I know of almost no studies that show an SSRI more effective in those patients. They are better tolerated, but I think that's where people miss the point. For the vast majority of patients Sherv Frazier used to call the "walking wounded," the SSRIs are good drugs. They are anxiolytic. They help despondent mood. They help mild to moderate depression. But for the more severely ill depression, the tricyclics, which were tougher to tolerate, were probably more effective.

TB: You had done some research on the side effects of tricyclics. Now what about side effects with SSRIs?

AS: They are much better tolerated and most of the side effects are gastrointestinal. About a year or year and a half ago, I participated in a study in which we compared sertraline and desipramine, and we found that men tended to be more responsive to desipramine and women had lower drop-out and better results, with SSRIs. So, there may be not just severity but also gender and estrogen levels relevant to effectiveness of SSRIs. There is now a European study on fluoxetine that also showed women do better with SSRIs. When, in 1988, fluoxetine came on the horizon, the reason it did so well was because there were a lot of women who couldn't tolerate or didn't respond to tricyclics. For men, the SSRIs are a mixed blessing; delayed ejaculation in men is more problematic and men may respond better in terms of mood to the tricyclics. There are some data, particularly on sertraline, that men are less responsive to sertraline than to a tricyclic.

TB: Did you do any research in bipolar patients?

AS: A little bit. We did less than we would have liked because McLean became specialized and the Kety, Lipinski, Ross Baldessarini group had done the bipolar research. When we did bipolar research, it was around bipolar depression, looking at catecholamines. We did do some work with lithium augmentation, lithium side effects, and things like that, but were less involved in bipolar research. Even to this day at Stanford, I don't do much bipolar research because I have a very good person, Terry Ketter, who heads up the Bipolar Program for us, and does the bipolar work. He has a couple of posters here as well.

TB: About the same time the SSRIs appeared in the 1980s, atypical antipsychotics were introduced. Would you like to comment on them?

AS: Atypical antipsychotics are very interesting drugs and I was fortunate at the Mass Mental Health Center, in 1988, to do some work with clozapine in collaboration with Alan Green and Jon

Cole that led to the publication of a couple of papers. In one paper, we reported a tremendous increase in circulating plasma norepinephrine in response to clozapine. It was probably because of its α_2 antagonism. We also did a study in the most severely ill, refractory bipolar patients, who were non-responsive to traditional neuroleptics, lithium, Tegretol (carbamazepine), or valproate and treated them with clozapine. We had about two-thirds of these patients dramatically better with clozapine. It took us about two-years to publish our results in the *American Journal of Psychiatry*. But it was one of the first reports on the use of an atypical antipsychotic in severely refractory mania. Now you have olanzapine approved for these patients. I think atypical antipsychotics are probably quite effective for acute mania. But the problem with atypical antipsychotics is they produce side effects that are problematic, mainly weight gain. Whether they cause Type 2 diabetes is in debate, but they certainly cause weight gain and that is problematic for maintenance treatment. But for acute treatment and people who do not gain weight, the atypical antipsychotics are very good agents. I forgot about those studies. Thanks for reminding me.

TB: Are you still seeing patients?

AS: I still see patients.

TB: So you are involved in basic and clinical research, teaching, clinical practice, and administration?

AS: Yes, and I run the department and the department runs me. I see patients Wednesday afternoon, when I'm in town and 400 or 500 patients I follow in consultation together with someone else.

TB: So you follow many patients?

AS: All with mood disorders. I teach residents, medical students, and run the department. I have been fortunate to keep up a very active research group with a number of interesting studies in animals and in man. We're doing a lot of functional imaging, particularly with glucocorticoid antagonists. I've been fortunate to be more productive, in terms of my research, at Stanford than at Harvard, and part of it has to do with the structure of the places. Stanford is very research oriented. Some of the Harvard programs are hospital-based, where Stanford is much more university-based and it's a lot easier to do research. I have people on our faculty and in our department to collaborate with, geneticists and people who do functional imaging. We're heavy users of the General Clinical Research Unit, where we do our HPA axis studies. I've been

fortunate, as a Chair, to be able to continue my own research because I have such good people around me. The job of the Chair has become more and more arduous with managed care, family practices, and hospitals stuff. What's been a godsend in my career is I don't think I've peaked in my research; a lot of people peak in their 40's. I'm 57 and I'm doing the most exciting work I've ever done and the most independent work. At Stanford, I have a large clinic but a small hospital service, so I can free myself up to do my own investigations.

TB: It seems that all through your professional career you have been working closely with patients.

AS: Yes, very closely. That's where you learn.

TB: Your activities are very well documented in your publications. You started to publish in the early 1970s and you keep on publishing. We have already talked about some of your publications, could you review those you consider most important?

AS: The papers on delusional depression and DST abnormalities published, in 1983, in the *American Journal of Psychiatry*, our papers on cognitive deficits published, in 2000, also in the *American Journal*, a paper on ACTH published, in 2000, in the *Archives*, a paper on psychotic depression published, in 2001, in the *American Journal*, and our mifepristone paper, published in October. Some of the other papers are just as important, as for example the paper on glucocorticoids versus dopamine in the *Journal of Neuropsychopharmacology*, the papers with Joe Schildkraut on MHPG, the papers on benzodiazepines and depression, some of our side effect papers, the paper on withdrawal hypomania, our pharmacogenetic papers, and our papers on imaging the hippocampus size in the monkey. We tend to be a bit contrarian, although to some extent our findings go along with what Strömngren referred to as reactive psychosis.

TB: Are you referring to Strömngren's postulation that reactive psychoses are based on genetic predisposition?

AS: Yes, that for reactive psychosis you need a predisposition...

TB: Would you like to say something about your books? You already mentioned the *Manual of Clinical Psychopharmacology* is going into its fourth edition.

AS: In 1988, with Charlie Nemeroff, we published one of the first comprehensive textbooks of Psychopharmacology that engulfs basic to clinical aspects of the field. We are now preparing the third edition of that text. We also did a primer of psychopharmacology that's in its first edition for the American Psychiatric Press. The textbook, *Essentials of Clinical Psychopharmacology* is

coming out in paperback. Charlie and I have been very, very pleased about it. I think it's a terrific book. It did not have the sales of the Manual. It's a much bigger book.

TB: Didn't you say that the Manual sold about 70,000 copies?

AS: Yes, 67,000. I think the first edition of the textbook did about 11,000. That is very good for a textbook.

TB: It's very, very good.

AS: The second edition sold 7 or 8,000 copies. Anything over 5,000 is a huge success. We've been very, very fortunate. The books are good. It has been fun working with Charlie. He's a very good friend.

TB: You have been awarded and received honors for your work. Would you like to mention a few?

AS: The awards I'm most proud of are the Best Teacher Awards I got from the Stanford residents right after I got there, the Klerman Lifetime Research Award, the Klerman Award from Cornell Medical College, the Strecker Award from the University of Pennsylvania, the Mood Disorders Research Award from the American College of Psychiatrists, and the award from the Northern California Psychiatric Society for Outstanding Achievement. In the military, I also got a Meritorious Service Medal. I've been blessed with this recognition and I am highly appreciative.

TB: You mentioned at the very beginning that you were in the Air Force?

AS: That's where I got that medal. They gave us the medal because they had to put up with us for a couple of years in those days. I was not exactly your typical US Air Force Major.

TB: When did you get involved with the American College of Neuropsychopharmacology?

AS: It was in the early 1980's I became a member; I've been coming to meetings for 20 years and it's the highlight of my academic year. The College is an incredible place. It truly is a College. We've witnessed transformation over time. We've been able to grow, and it's been just a wonderful, wonderful experience.

TB: You were president of the College.

AS: I was President in 2000, and after the business meeting in a couple of hours, I will be the immediate Past President and Chuck O'Brien will be President. I was on the council for three years and took a year off before becoming president elect. Seven out of the last eight years, I've been very involved with running of the organization. It's a unique place. It is a place of

tremendous friendship, tremendous collegiality. You see your friends and see them working on scientific issues important to the field. The College has been enormously successful. The Nobel Laureates last year are important additions to Julie Axelrod. It's an organization that has meant a lot to me in my professional life. I've been on the program many times, although not every year; we usually present every two or three years. And we usually do a panel every couple of years. This year we're on two or three panels because I organized one on substance P and we have a panel on delusional depression this afternoon. We also have a few posters. It's a wonderful place to see people and the one meeting I look forward to. I go to a lot of meetings every year, but this is the one that really means something to me.

TB: Is there any other organization you have been involved with?

AS: I belong to the American Psychiatric Association, the American College of Psychiatrists, and the International Society of Psychoneuroendocrinology. I serve as their Secretary General. But, the International Society of Psychoendocrinology is a much smaller Society. It's very, very specialized. It certainly fits an area of my interests, but I have other interests as well. Still, there's nothing like ACNP. It's small enough to have fabulous meetings but large enough to include people of many different disciplines. One of the things Steve Paul, when he was President, started was looking at the holes in the College and trying to fill them in. We've been trying that actively this year, adding some child psychiatry researchers and others in research methodology and statistics. We need to find and add people in certain areas, to keep ahead of the cutting edge and I think we'll do it. It's a College that you were involved in earlier with Jon Cole, Frank Ayd, Heinz Lehman, and others, in founding the organization. We owe all of you guys a tremendous debt of gratitude for having the vision to come up with it. Since 1961, science has changed, but the quality of the College hasn't. The quality always was superb and continues to be.

TB: Is there anything else you would like to add or comment on?

AS: Psychopharmacology has been a godsend when I think of patients I saw when I started in psychiatry. It was a big switch from imipramine to amitriptyline. Then we got into MAO inhibitors, which were great drugs, effective for lots of patients, but dangerous as hell. Now that we've got so many tools, we're starting to understand the brain. But we have some real holes, for example the nomenclature we use, the classification we have. The changes will come through genetics and other techniques rather than through descriptive classifications. We mentioned that

the diagnosis of major depression is too broad. We have a lot of people who meet criteria but are not really depressed, and that's something we're going to have to solve. The DSM has been helpful in providing a cross-practitioner language people could agree on, so it's reliable but it's not clear it's valid. To make that next move, hopefully clinical biology will come up with innovative treatment strategies. We hope our work in psychotic and delusional depression is in that genre. It seems to me it is, but it depends whether we can convert it to an effective treatment. That's the kind of thing we need to do, so we can then have a better and more effective psychopharmacology. So that's the message I would like to leave in 2001.

TB: So, you're concerned about the nomenclature.

AS: It needs to be hooked up with genetics. We need a functional nomenclature that goes with genetics to develop new drugs. At the same time, even though I'm a psychopharmacologist, I believe in psychotherapy and the combination of therapies for most patients. Most patients need some sort of combination treatment and that needs to be taught. I'm concerned that some departments are moving away from it. You can debate whether we should be teaching more dynamics.

TB: Do you think we need to teach psychotherapy?

AS: I've been involved with Marty Keller in some very elegant studies on chronic depression. We published some papers looking at nefazodone in combination with a cognitive behavior therapy called CBASP and are now going to do another multi-center chronic depression study, hopefully, funded by the NIMH. So I still believe in psychotherapy and I think it's important. I also think we need to study the biology of it. As we do more clinical biology, we need a little more gender-based sophistication. Our studies in chronic depression suggest gender plays an important role in drug response in premenopausal women. We need to understand that.

TB: You are involved in psychotherapy research as well?

AS: We still do psychotherapy and psychotherapy research in depression.

TB: What other interests do you have outside of psychiatry and psychopharmacology?

AS: I'm an avid reader, but I read practically no fiction. I love books about history. I love reading about sports, adventure, mountaineering, and things like that. We travel a great deal, not only for business but for pleasure. We like the fine arts. I like the theater, and I'm a big sports nut. In the last few years, I started to play golf, which is my nemesis although I enjoy it. And I like coming

to Waikoloa because I get to play golf sometimes during the meeting, although when you're on the council it's a little tougher. Those are my hobbies and they keep me busy.

TB: Do you have a family?

AS: I have a wife, who I met at Mass Mental Health Center, and who was a psychiatric nurse and became a psychiatric social worker. I have two daughters, one who is in law school and one who just graduated. Neither of them is married.

TB: Is there anything else you would like to add?

AS: No. Doing these interviews is an important thing Tom; we appreciate your dedication to the College and are indebted to you for developing this archival material.

TB: On this note, we conclude this interview with Alan Schatzberg. Thank you very much, Alan.

AS: Tom, thank you.

56. NINA R. SCHOOLER

TB: We are at the Annual Meeting of the American College of Neuropsychopharmacology in Hawaii. It is December 11, 2001, and I will be interviewing Dr. Nina Schooler⁵⁸ for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. So, let's start from the beginning. Could you tell us where and when were you born, about your early interests, and how you got into neuropsychopharmacology?

NS: It's a pleasure to be here and interviewed for the Archives. I was born in New York City, in 1934, and was educated in New York City public schools, with the exception of a few years when I lived in Miami Beach, Florida. I graduated from the Julia Richmond Country School, which was not in the county, but located on the east side in Manhattan, and then went to CCNY, the College of the City of New York. I was fortunate to be in the first class to which women were admitted to regular college other than to the college of education or the business school. I graduated from CCNY with a BSS degree, Bachelor of Social Science, in 1955, and went to work at a company called The Psychological Corporation, working in market research and coordinating the researchers who collected data for The Corporation. And, as I look back on my career, that's what I've been doing ever since; coordinating the collection of data. I entered Columbia University in 1956 to get a Ph.D. in Anthropology. My undergraduate major had been Sociology. It appeared to be a bad mix between marriage and Anthropology, which required travel to faraway places. So, I switched to an interdisciplinary program, Social Psychology, and completed my course work in a very expeditious fashion. Then, in the 1950's, my husband obtained his Ph.D. and we moved to Bethesda, Maryland, where he had accepted a position in the intramural program of the NIMH. I became a stay at home wife, working on a doctoral dissertation. At the same time, I had a baby and maintained contact with my doctoral advisor at Columbia, Richard Christie, a very well-known Social Psychologist, who was supportive, but not particularly helpful, in what topic to choose for a dissertation. At that time, when my son was about two years old, I was told about a

⁵⁸ Nina Schooler was born in New York, New York, in 1934. After she received her PhD in Social Psychology from Columbia University in New York City, New York, she received a position at the Psychopharmacology Service Center of the National Institutes of Health in Rockville, Maryland. She left NIMH to join the faculty of the Department of Psychiatry of the University of Pittsburgh in Pittsburgh, Pennsylvania. Subsequently, she joined the faculty of the Department of Psychiatry at Zucker Hillside Hospital in Glen Oaks, New York. She was interviewed in Waikoloa, Hawaii on December 11, 2001.

position at The Psychopharmacology Service Center of the NIMH. I was directed to call Solomon Goldberg, and the rest is history. That was the most useful phone call I ever made. Sol hired me as a research assistant, part-time. I was only willing to work part-time, because I had a small child turning three and starting nursery school. My view was that I would work when he was in school, and when he wasn't, I would be home with him.

TB: So, you started as a part-time research assistant?

NS: Sol later told me he had wanted a full time assistant and somebody who had a Ph.D. He turned out to be the most wonderful boss, collaborator, and mentor. The PSC was headed by Jonathan Cole, who was the most creative leader of a new field anyone could have imagined. This would have been 1962-63. The Service Center was new and Jonathan assembled a remarkable number of investigators in pre-clinical and clinical psychopharmacology, although nobody had a name in the field, at that point. The NIMH then was a looser organization than it came to be later and Jonathan's creative juices were allowed to flow. He was able to do all sorts of wonderful and inventive things, in terms of distributing money to the field, mechanisms for providing support to do studies and so forth. When I arrived at the NIMH-PSC, the first collaborative study had just begun. This was a nine-hospital study, comparing three phenothiazines to placebo. Jonathan Cole and Gerry Klerman, who had been at the PSC for a couple of years, designed the study, Sol Goldberg coordinated it, and I was his assistant. My background was in Social Psychology, so I didn't know anything about psychopharmacology. I knew a little bit about methodology, not clinical trials, but experimental methodology. I understood the principles of randomization and a few other things, but not anywhere near as much as I learned over the next several years. Yet, because the field was so new and things were so open, I had lots of opportunity to do literally as much as I wanted. If I stumbled, someone would help, so it was a wonderful, wonderful opportunity. I can't stress enough the richness of the environment at the PSC and outside. But, not having my degree, I was pretty well invisible person in the organization. While I was allowed to do what I could within the organization, beyond it I was invisible. There was a lot of support for me to develop a doctoral topic related to what I was doing and enable me to obtain my degree. The system at NIMH allowed me time to write when I needed to write, to develop a data collection plan and to collect the data. At the same time, a wonderfully supportive faculty person at

Columbia, while recognizing this was not an area of his expertise, was prepared to sponsor my dissertation.

TB: What was your dissertation on?

NS: The topic I chose was one which had nothing to do with psychopharmacology; it involved schizophrenia, the patient population of the first NIMH collaborative study, which has remained an area of interest from 1963 to this date. In some ways, that was happenstance. That was where I happened to fall, but in many ways it was an extraordinarily lucky opportunity, because schizophrenia was a fascinating disorder and remains so for me, today. My dissertation dealt with language in schizophrenia; I looked at grammatical linguistic distinctions and compared performance on a test I devised with schizophrenia patients and normal controls, matched for education. It's one of the embarrassments of my career, that the results have never been published anywhere, except in dissertation abstracts. I suppose that's because of the career direction I took. I have never thrown away the data and they probably still have relevance to the field of language and thought disturbance in schizophrenia. Maybe I'll get back to them one day. I obtained my Ph.D. in 1969, when I was thirty-five, several years after my bachelor's degree. Here I want to digress for a moment to comment about the status of women in the field, at the time.

TB: Please do.

NS: In some ways, the status of women was easier in the 1960s and 1970s than it is today. Perhaps I can explain that by saying it was a time of low expectations. There's a line, I think, by George Bernard Shaw. When asked about women preaching, his comment was, "It's like a dog walking on hind legs. You admire the fact that it does it and don't comment on the quality." And, in a sense, that the situation for women. For example, if you look at my C.V., you can see a gap between 1955 and 1969, from my bachelor's degree to a Ph.D. In the case of a man, the question would be what happened during that period? Why didn't he get his degree more promptly? Is there something wrong with him? For a woman no one would bother to ask those questions. One year of the delay, between 1968 and 1969, could be attributed to the fact that my dissertation was locked up at Columbia University in the mathematics building, because of the 1968 student riots, so my sponsor was unable to review it. When, finally I received the degree, in 1969, I was admitted to full status in the PRC. Rather than just working within the department, I was eligible and allowed to interact with the wonderfully burgeoning field of clinical psychopharmacology on the

outside. One of Jonathan Cole's innovations was to create an external committee that reviewed grants in clinical psychopharmacology. He had done this because when grants that tested whether there was a difference between two drugs went before the standard study sections at NIH, they did very poorly. The PSC had been established with money that was supposed to fund these trials. So, Jonathan had a mandate and needed a mechanism to allow him to fulfill it. And this review committee was one of the major mechanisms he established to do that. Now I had a Ph.D. and could be addressed as Doctor, I was acceptable and presentable as a member of the staff at study section meetings. So, I started to get to know colleagues in the field. So, it was in, I believe, 1970, I had my first opportunity to go to an ACNP meeting, held in San Diego. Sol Goldberg, who was still a close colleague, working together, invited me to the meeting to participate in an ongoing study, called Prediction of Response in Schizophrenia. He and Jim Klett were responsible for it and the group met throughout the meeting and persisted from year to year.

TB: What did you present on?

NS: I don't remember, although I believe it had to do with the use of what we called performance tests, which are now known as neuropsychological or cognitive measures in schizophrenia. They were data from a second, longer term, collaborative study Sol had been instrumental in designing and I was involved in the conduct of. What I remember about the meeting are two things. First, the plenary session was on the topic of cyclic AMP and I sat for an entire morning understanding only the connector words in the sentences. I had no knowledge of what the meaning of the nouns was and no understanding at all of what was going on. My feeling was that this was a place that was not for me. I then participated in a study group in a relatively small room. There weren't more than fifteen or twenty people in the room; some of them I knew, and they smiled and said "hello." The others also seemed friendly. Everyone was very absorbed in the discussion; it was very collegial. I left for home with the feeling that, overall, the organization was vastly beyond my comprehension, and a sense I had been in an environment that was much bigger than I knew or understood. I have been part of the ACNP since that time, and some of that feeling of awe, of being part of something much bigger than I know or understand, persists. It is as though, even as my own knowledge base grows, the field grows more rapidly than I do. I still have some of that feeling, but nevertheless go to the plenary sessions and sometimes they work but sometimes they don't. This year's plenary session, I'm leaping from 1971 to 2001, was a good one for me and I

attribute it to the organization of the topic, which was on substance abuse, and the quality of the speakers.

TB: I see.

NS: Now, I suppose I should go back to 1971, where I had found what felt like a very valuable and important niche within the PRB at NIMH. And that was in the design and coordination of multi-center studies in schizophrenia, and here I'll ask whether it's appropriate to describe the sequence of studies I was involved with?

TB: Of course.

NS: There were a series of studies I worked on from 1971 to 1988, the year I left the NIMH. They were all on schizophrenia; they all addressed important questions and they were all studies which were difficult to carry out, so people were not likely to do them on their own. I've already talked about the first study, the one designed by Jonathan and Gerry Klerman, well before I got there, in which three phenothiazines were compared to placebo in a short six week trial. The second study, which was designed by Jonathan and Sol Goldberg, looked at the long term effects of three phenothiazines with no placebo, given that the placebo control question had been answered. This was followed by a study that Sol and I did, in collaboration with Sam Gershon. It dealt with prediction of response and was designed to compare differential clinical profiles of patients responsive to two different phenothiazines. Then we went on to do a study with Jerry Hogarty that started one of the other strong interests I've had, in long term treatment and the interaction of psychosocial and pharmacologic treatments in schizophrenia. This was a two year study in which we compared chlorpromazine to placebo and to a psychosocial treatment, called major role therapy, or no psychosocial treatment. After that, this would have been about mid 1970's, Sol retired from the NIMH, to move to the Medical College of Virginia, and Jerry Hogarty and I went on to do a study in which we looked at the interaction of fluphenazine, long acting and oral, with psychosocial treatment. In a parallel study, Jerry Levine, who had taken over directorship of the PSC-PRB, and I designed and carried out a collaborative study. I believe it was done in four sites, where we compared injectable fluphenazine to oral fluphenazine in a one yearlong study. This four center fluphenazine decanoate study and the one in collaboration with Hogarty were the first ones where I had principal responsibility for design, conduct, and coordination. I'd been doing the coordination for a number of years and that was more facilitative, carrying out tasks, but these

were studies where the questions came from my thinking about the nature of the illness, and what the important treatment questions were. These were wonderful, wonderful opportunities for me.

TB: Could you tell us something about the results?

NS: Absolutely. The original first collaborative study showed the dramatic effects of three phenothiazine medications compared to placebo in six weeks. This was certainly not the first study to show that. There were certainly studies in the field which showed similar findings. What was important about this study was that it was in hospitals where people said it didn't matter if you gave people drug or placebo; places like the Institute of Living or Paine Whitney Clinic, which had wonderful clinical programs. The idea at the time was it only mattered in State hospitals, and this study showed the effects were uniform across all hospitals. The finding we had out of the second study was we could not distinguish among the drugs, but there were increasing effects out to six months. That was a very valuable contribution because it suggested the drugs were not short term, but there were long term effects that made a real difference in the lives of patients. There were also collaborative studies done in the Branch I was not involved with, which were long term in very chronic inpatients, while the initial studies had been done in acute patients. The first study had been designed for first episode patients, but when it turned out to be difficult to accumulate first episode patients, they changed the inclusion criteria to acutely symptomatic patients. The two year maintenance study that Sol and I did with Jerry Hogarty represented for many years, and possibly still does, the best demonstration of long term medication effects in schizophrenia. When people are looking for an estimate of the placebo response rate in schizophrenia over the long term, what is often cited is the non-relapsed placebo response rate after two years in that study, which was about twenty percent. Essentially, what we found was that medication represents a platform against which psychosocial treatment can operate, because in the patient group that received placebo, the intensive psychosocial treatment turned out to be deleterious; that was a very important finding, but not one that was immediately recognized. In our studies of long acting fluphenazine decanoate and oral fluphenazine, we were unable to find a difference between the two, which represented a great disappointment to many people in the field because the findings meant that compliance didn't make a difference. It was contrary to what every good clinician knew, namely that patients who don't take medication, relapse. We should have known, with hindsight, that the kinds of patients who agree to participate in a clinical trial are likely to be more

compliant than the rest, so the study was biased against finding a difference. What we did find that had a major impact on my understanding was that even when patients take their medication exactly as prescribed, they can relapse.

TB: Very much so.

NS: Let me talk about my other activities at NIMH, because this was the research part and, in many ways, very fulfilling, but not the only thing I loved about my job.

TB: Please do.

NS: One of the things I loved was the fact I had the opportunity to interact with a broad field of people in psychopharmacology, beyond the members of ACNP, because our group was involved in reviews and administration of grants that came from the outside. One of the things that has been the most fun is to see people I knew as young beginning investigators, mature, become my colleagues, and go on to very illustrious careers; now one of them is my boss!

TB: Could you mention a few of these people?

NS: When we compared fluphenazine decanoate to oral fluphenazine, Allen Gellenberg, who's now the Chair at the University of Arizona, was finishing a residency and starting as a research psychiatrist. He has become a colleague and friend over the years. In a more recent study, a young psychiatrist, Peter Weiden, also a resident when we started the study is now ready for promotion to Professorship with tenure at Downstate in New York. Then, in the last study I did at the Institute, "Treatment Strategies in Schizophrenia," I worked with Sam Keith, someone I met when he was a young Fellow joining NIMH.

TB: When did you leave NIMH?

NS: I left NIMH in 1988, in the middle of the study, not as a retiree but as a resignation. The reason was that I was ready to move out from a protected environment, in which I had grown up. I wanted to see whether I could make it in the real world. The first question was that I needed a job, so I put out a couple of sort of tentative feelers, to find out if there were any appropriate positions for me in the academic world, within an hour airplane radius from Washington, D.C., where my husband was. You can get to a lot of places in an hour from Washington. Another reason I wanted to make this move was difficulty in relationships with people in the field when you're in the extramural program of NIMH. Most decisions are made by review committees, and

there were enormous checks and balances on the power of any given individual. I often had the sense people didn't believe me when I told them that.

TB: Where did you move?

NS: I took a position at the University of Pittsburgh in David Kupfer's department, directing a Psychosis Research Program, where, as David explained to me, "Whatever it is you do will fit within the parameters of psychosis research." He couldn't give me the word, "schizophrenia," because that was already taken! I moved to Pittsburgh and because of the wonderful collaboration with Sam Keith and a junior colleague and biostatistician, Joanne Severe, at NIMH, I was able to continue as primary director of the treatment strategies in schizophrenia study. That was wonderful because it was a study I was devoted to; I'd like to think it was also wonderful for the study, because we did carry it successfully to completion.

TB: Could you tell us about the findings in that study?

NS: We used fluphenazine decanoate because that was the only way to guarantee our dosage comparison would not be diluted by noncompliance. We found the rate of relapse was quite low with the moderate dose of fluphenazine decanoate, that there was an increase in relapse with the low dose, and with the group that only received "rescue medication" at signs of prodromal symptoms, the relapse rate was substantial. We couldn't distinguish re-hospitalization rates between moderate and low dose groups, but we saw an increased rate of re-hospitalization with the prodromal sign intervention group which only received medication if needed. What that means is that when a low dose is used in maintenance and raised when there is symptom exacerbation in outpatients, it's possible to avert re-hospitalization. But, if there's no medication, as in the group that received medication only as needed, even an adequate dose of medication given at the initial symptoms, is not enough. This was in the context of an elaborate treatment team approach with families, because in order to be in the study, patients had to have a family member available. This was why we were prepared to take the risk of an early intervention strategy, because we had both a treatment and a family team in place. The other point that was significant was that the length of treatment exposure, two years, was critical to demonstrating these effects. If our study had only been three months long, we could have seen none of the medication treatment effects. If it had been one year long, we would have said the moderate dose was better than either the low or early intervention strategy, but we could not have distinguished the low dose group from the early

intervention group. So, it was only by going out to the second year, could we successfully discriminate the three medication conditions.

TB: Now, it is 1988 and you had moved to Pittsburgh.

NS: When I moved to Pittsburgh, a decision I made independently, both of my sons had made the same decision the year before. One was a beginning assistant professor in the Psychology Department at the University of Pittsburgh and the other was a beginning graduate student in Psychology at Carnegie Mellon University. While I had moved away from home, I had gone to the same place my sons were, so I had a very strong support network in Pittsburgh. When I arrived in Pittsburgh I had two interests I knew about on arrival, and both were at opposite ends of the spectrum in schizophrenia. One was in first episode schizophrenia. Since the original NIMH collaborative study, I was strongly interested in the question of what happened in schizophrenia if one examined it from the beginning?

TB: And the second one?

NS: The second was in chronic and refractory schizophrenia. So, within a month of my arrival, in early 1988, I went to visit Mayview State Hospital, about fifteen miles and twenty-seven and a half minutes from Western Psychiatric Institute and Clinic, where I was based. The reason I can tell you, with such precision, how many minutes it took was that I made that trip virtually every week over the next ten years. We were able to establish a research ward with the support of the State and the Institute, so this was a collaborative effort between the University and the State facility. I had wanted to call the unit the Center for Community Asylum Treatment, intending the little “a” meaning of asylum, a safe haven. Nobody would allow that title. Everyone thought it was a terrible idea that was going to get us into real trouble. So what we finally called it was the Special Studies Unit, which everybody agreed to. We were certainly “special” and they allowed the word “studies,” and that’s the name of the unit to this day. What we were able to do in that environment was very, very positive. This was 1988, about the time the study with clozapine had been completed by John Kane, Herb Meltzer, and their colleagues. Since the Mayview Hospital had been one of the sites, there was enormous enthusiasm for new treatments. So, within six months of arriving, I was offered the opportunity to participate in the study of risperidone that Janssen was conducting and this was my first industry sponsored venture. I had the good fortune

of being in a place at a time where I could become actively and enthusiastically involved in the research on atypical or second generation antipsychotics.

TB: Could you tell us about the study with risperidone?

NS: Four doses of risperidone, haloperidol, and placebo were compared and all doses, from six to sixteen, were better than placebo. Haloperidol was also better than placebo. Haloperidol turned out to be a side effect disaster, in terms of extrapyramidal signs. That was because the dose was twenty milligrams a day. At the investigators meetings, I tried to recommend the dose of haloperidol be changed, because I thought it was too high. As I subsequently learned, investigator opinions are not seriously considered by industry. They may be noted, but they're not wildly encouraged. But what was useful from my perspective was I learned how to contribute more directly to later studies, one in particular. This was a first episode study, also with Janssen, for which I was the lead investigator and compared risperidone and haloperidol, using haloperidol in appropriate dosages.

TB: How was the dose determined for the first episode study?

NS: On an a priori basis. The study is just finishing data collection. It was a double blind study in which doses of the two drugs were determined in milligram equivalents. In this study, the milligram equivalent of risperidone and haloperidol was one to one, and the target dose for both was four milligrams. The investigator was free to use as many or as few of the capsules as desired, although there was an initial titration schedule. The reason I was asked by Janssen to work with them on this project was because we had developed a very excellent and elegant program in First Episode studies at Pittsburgh. This was in the context of a Center for Neuroscience and Schizophrenia, funded by the NIMH, for which, first Ed Streicker, and subsequently, David Lewis, have been the directors. Because the Center was supposed to be translational, involving integration of clinical and basic research and required a clinical arm, I was recruited to represent that. We decided the area we wanted to look at was first episodes so we designed a series of longitudinal studies.

TB: With whom did you collaborate in this study?

NS: My major collaborator was Matchei Keshavan, who continued to direct the studies after my departure. These were not traditional clinical trials. The design was longitudinal evaluation with treatment provided by the study team following an ideal approach that's been used in many other

First Episode studies, in particular the Hillside Hospital study led by Jeffrey Lieberman, before he left for North Carolina. We followed a very low dose paradigm based on the work Joe McEvoy had done at the University of Pittsburgh, in which he looked for a neuroleptic threshold dose with haloperidol, based not on the Haase handwriting model to detect early hypokinesia. He found, in first episode patients, the neuroleptic threshold was in the neighborhood of three to four milligrams with haloperidol, which we used in our early work. When risperidone came out in 1994, we were not able to use a neuroleptic threshold dose, because for risperidone it is much higher. So, we dosed on an empirical basis, starting at one milligram, with a target dose below four milligrams. In our early work, we found the dose for risperidone was very similar to haloperidol, at about four milligrams, and that was why that dose was chosen in the Janssen trial, for which the results are unknown at this point. The model for the work we did with the first episode patients at Pittsburgh provided clinical assessment and ongoing monitoring of patients' cognitive functioning and, if feasible, included brain imaging. It was an enormously productive program because of the importance of first episode studies, particularly in patients with no exposure to antipsychotic drugs. Such studies allow us to understand manifestations present from the onset of the disease, as opposed to manifestations that may be confounded with later stages and effects of treatment. Some of our findings were counter to my intuition regarding brain structural and functional abnormalities, which I believed were a function of chronicity and treatment. They turned out to be more characteristic of neurodevelopmental abnormalities that occurred earlier, since many of these were present at the onset of the disease.

TB: Did you get involved with any newer antipsychotics other than risperidone?

NS: I have had the opportunity to participate in trials and served on advisory boards for the companies developing many of these drugs. One of the drugs I was involved with was sertindole, the Lundbeck compound licensed to Abbott in the United States. At our Special Study Center at Mayview Hospital, we were also involved in a couple of studies of quetiapine, (Seroquel) with AstraZeneca, but I've not had any direct involvement with that company. I've also been involved, since 1998, after I left Pittsburgh for Hillside, with Pfizer in the development of ziprasidone. Finally, I've been involved in the development of aripiprazole, originally, with Otsuka, the company that developed it, and then with Bristol Myers Squibb. My ties with Otsuka were closer; I was involved in the design and development of a couple of their studies. Those have been

wonderful experiences. I have also served on an advisory board for Lilly regarding olanzapine, before it came to market. I have a little paperweight to prove it, which has on it Zyprex, which was the name that it was given before Zyprexa. I haven't decided whether to take that to the Antique's Road show, but maybe sometime later! I think the new antipsychotics are really exciting and I'm most interested now in long term treatment, because I think we don't know how they work until we understand how they'll do in the long term.

TB: When did you move to Hillside?

NS: In 1997, when John Kane, whom I had known since residency, and is now Chair of the Department at Hillside, invited me to become the Director of Research. I swallowed long and hard, but it seemed a very exciting opportunity to direct a broader program than I was working with at University of Pittsburgh. I accepted and the way I described my move is, it was from Hawaii to Hillside, because after the last ACNP meeting here in Waikoloa, in 1997, I went back to Pittsburgh, packed my bags, and moved to New York. That's where I've been since and the opportunities there have been terrific. First, one of the opportunities has been to work closely with John Kane; although we worked together before in the Treatment Strategies and Schizophrenia Study. When I arrived, there were many people in the group that I had worked with and other people I had known from even earlier times, because of my long collaboration with Hillside in the area of tardive dyskinesia.

TB: Could you tell us about your activities at Hillside?

NS: I'm doing three things at Hillside. One is related to a project I started at the University of Pittsburgh shortly after I left NIMH. With Steve Marder at UCLA and John Kane at Hillside, we compared clozapine and haloperidol and found, as we published just earlier this year, that in six months, clozapine was dramatically better than haloperidol in any way we looked at the data. In a second study that we started when I was still in Pittsburgh, we compared clozapine and risperidone. We completed this study after I moved to Hillside and we're in the process of analyzing those data. So, that is one of the three projects I have been involved in here. In this study, of which I reported the results in a poster, we found the distinctions between risperidone and clozapine are nowhere near as sharp as those between haloperidol and clozapine. There are definitely advantages for clozapine, but also for risperidone.

TB: What about the other two projects?

NS: We have ongoing a new First Episode study in which we are comparing the effects of risperidone and olanzapine up to three years. The principal collaborators are John Kane, I, and Delbert Robinson, a newer investigator. In addition, I'm involved in another collaborative study looking at negative symptoms in schizophrenia, collaborating with Will Carpenter at the University of Maryland, Dan Javitt at NIMH, and Steve Marder at UCLA. We are looking at NMDA agonists in the treatment of negative symptoms.

TB: Your activities from the very beginning are well documented in your publications. Could you say something about your papers? What was your first paper?

NS: My first publication grew out of the first NIMH collaborative study. Its title was something like, "One Year after Discharge, Long Term Outcome," I don't remember the rest. It was the first formal presentation I ever made at a meeting, at an annual meeting of the American Psychiatric Association. It documented the long term outcome in patients who were receiving follow-up. What was most instructive is that we found benefits in patients who had received placebo in the short term trial. We interpreted the finding, and I still think it's the best, that patients who received placebo had slightly longer hospitalizations, during which they received extraordinary care that left them better prepared to return to the community.

TB: When and where was it published?

NS: In 1967, before I received my Ph.D., in the *American Journal of Psychiatry*.

TB: What was your most recent publication?

NS: The most recent is not a first authored publication, but I'm prepared to take major credit for it, because it was an equal collaboration. This was with John Kane and Steve Marder reporting on the clozapine and haloperidol comparison. It came out in October 2001, in the *Archives of General Psychiatry*.

TB: What would you consider as your most important publication?

NS: The paper I'm proudest of was the one that reported the "Treatment Strategies in Schizophrenia Study," which was in the *Archives*, I believe, in 1997.

TB: What would you consider as your most important contribution to the field?

NS: It would be the emphasis on the study of long term treatment in schizophrenia and the importance of looking at long term treatment effects. A second one I haven't even commented on

is the importance of looking at outcome measures that go beyond psychopathology. I've worked on the development of rating scales to assess social adjustment and see that as a contribution.

TB: Any other contribution you would like to mention?

NS: I think I'm a really good collaborator and mentor. It was already in my grade school report card that, "works well with others."

TB: Could you say how people responded to your findings at the time you published them?

NS: Our findings in the "Treatment Strategy in Schizophrenia Study" were readily recognized as a definitive statement regarding antipsychotic treatment in schizophrenia and what the limits of treatment are. On the other hand, the response to some of our findings with family treatment were extremely negative and have been criticized, both in private and public, on the grounds we didn't do it right. That's OK with me, because it's my belief we did it right and the findings stand.

TB: Let me switch to something entirely different. When did you become a member of the ACNP?

NS: 1975.

TB: Would you like to say something about your ACNP activities?

NS: I was admitted in 1975, one of three women admitted that year. The other two were Magda Campbell and Jean Endicott and we doubled the number of women in the College. I have had extensive committee involvement, in two committees, in particular. I was on the Education and Training Committee, chaired that for a couple of years, and it was a wonderful experience. I enjoyed meeting the young people, whom I still see at the meeting today, and felt very positive about that experience. I'm currently on the Credentials Committee. That's a very challenging experience. It is far harder to get into the ACNP today than it was in 1975, and I'm constantly dismayed at the number of people we do not admit, who might well turn out to be very positive contributors to the society. It's a tribute to the ACNP that people want to be members and I'm happy to serve in this role, but I will also be happy when I get to stop.

TB: Am I correct you are still fully active?

NS: Oh, yes.

TB: And you seem to intend to keep on going.

NS: That's absolutely correct. I see myself as busier than ever.

TB: I would like to wish you the best with your work. Thank you very much for sharing this information.

NS: It's been an absolute pleasure. Thank you very much.

57. CHARLES R. SCHUSTER

TB: We are at the 38th Annual Meeting of the American College of Neuropsychopharmacology at the Acapulco Princess in Acapulco, Mexico. It is December 13, 1999, and I will be interviewing Dr. Charles Schuster⁵⁹ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Can we begin with where you were born and when? If you could say something about your family, educational background, and then, we can move on from that.

CS: Well, I was born in 1930 in Woodbury, New Jersey. My mother and father were both, I would say, very inquisitive, intellectually inquisitive people. My mother was a musician and influenced me very, very much in my early career choice to become a musician. On the other hand, my father had been in the medical corps in the first World War and when he got out, he decided that he wanted to go into some branch of medicine, but he became very intrigued with a branch of medicine, at that time, which was called Naturopathy, which interestingly enough espouses principles, which we today would call Holistic Medicine or Preventative Medicine. As a child, for example, I never had candy until I went to school, because it was not in my home. We had very little salt. We had a variety of dietary restrictions, which were based upon principles of health, and I think, probably, have served me well, because I'm probably much healthier because of it. My father got out of that profession for a variety of reasons, not the least of it for which it was nice, financially, and went back into his family business, which was in the food business. But, I was very much influenced by his interest in health issues and his interest in the relationship of diet and lifestyle, etc., to health. Well, my mother was, as I said, a music teacher and a musician and I began, by the age of 5, to play trumpet. I had an older sister, who was seven years older than I am, and by the time I was 10 or 11, she was 17 or 18, and going to a college in the area. My sister was a very beautiful young woman, who wrote poetry and liked jazz, and a lot of the jazz

⁵⁹ Charles R. Schuster was born in Woodbury, New Jersey, in 1930. After military service, he received a master's degree in psychology from the University of New Mexico. He, subsequently, worked as a technician at the pharmaceutical company, Smith, Kline and French. He received his doctorate in psychology from the University of Maryland. After his initial appointment in the Department of Pharmacology at the University of Michigan, he joined the Departments of Psychiatry, Pharmacology, and Behavioral Sciences and founded the Drug Abuse Research Center at the University of Chicago. In 1986, Dr. Schuster was appointed the Director of the National Institute on Drug Abuse, a position he held until 1992. He then joined the Department of Psychiatry and Behavioral Neurosciences at Wayne State School of Medicine and served as Director of the Addiction Research Institute. Dr. Schuster died in 2011. He was interviewed in Acapulco, Mexico on December 13, 1999. Schuster died in 2011.

musicians, who would come to Philadelphia and the Camden area where I was living, were very interested in her, because she was very attractive, and she would invite them to come to our house on Saturday afternoon. We had, of course, a large grand piano because my mother was a music teacher and some of the top jazz stars of the 1940's, came to my home on Saturday afternoon and would play. Well, I was a little kid. I was 12, and they would say, oh, you've got a trumpet there, why don't you play with us? So, I started playing with some very noteworthy people at a very early age and I'd been studying trumpet since I was five, so, you know, I could play. I started playing in nightclubs by the time I was 13 and didn't spend a heck of a lot of time on my high school studies. I will be honest about that. I spent more time playing jazz in nightclubs and continued to do that throughout high school and, as a consequence of that, I couldn't get into a very good college. So I went to a local community college and continued to play jazz until I was about 18, at which time I became very frightened, because many of the young musicians that I had grown up with and was working with had passed beyond smoking marijuana and had started to inject heroin. Frankly, it scared me to death, and I retired, essentially, from the music business at about the age of 18 or 19, because I could not see myself going down that pathway.

TB: What did you do after that?

CS: I, then, began to get a little bit more serious about school, and got through my community college with sufficiently good grades that I was able to get into Gettysburg College, from which I graduated in 1951. My sister had gone to college and she was interested in Psychology, and so, when I started college, I found Psychology to be, not only of interest, but perhaps, easier for me, because she had taught me a lot about it and, so, I just gravitated into studying, both Psychology and Biology in my college career. When I got out of college, which would have been in 1951, my sister was married and she was married to a great guy, who had just gotten out of the Marine Corps, and I thought, boy, wouldn't it be neat if I could follow his career? I'm going to enlist in the marines. Well, I went over and, you have to understand in 1951, if you didn't enlist in the Marine Corps, you would be drafted in the Army. So, I decided I would enlist in the Marine Corps and I went through all the physicals, was accepted directly into becoming an officer, because I had a Bachelor's Degree from Gettysburg College, and it was then that they discovered that they had not done a dental exam on me, so I went through the dental exam and I was missing one molar on one side, and they said, sorry, but you cannot become a Marine Corps officer unless you are physically

perfect and missing one tooth disqualifies you. So, there I was, I was not going into the Marine Corps. I hadn't made plans for graduate school, but I knew someone who was going out to the University of New Mexico where they had a master's degree program in Psychology and I decided that, well, maybe they will take me, and I called up and I talked to the Chairman of the department. I guess I must have convinced him that I should go there and he, fortunately, admitted me, even though I hadn't gone through all the usual procedures. So, I went to the University of New Mexico, and entered their graduate program. I had a teacher, by the name of George Maxwell Peterson, and nobody that I know of could have made the neuroanatomy and neurophysiology of the central nervous system more exciting than he did. He did rat studies in terms of how cortical lesions would affect various complex performances like maze performances, and I decided, well, you know, that's what I will do. For my master's thesis, I severed the corpus callosum in rats and looked at a variety of tasks, including tasks of handedness. One of the other interests that Dr. Peterson had was in the cortical region that controlled handedness, and he'd shown, many years before, that the destruction of as little as 3 percent of the cerebral cortex on the dominant side in the right region could convert a right handed rat to an ambidextrous rat. Well, he wondered whether or not if we severed the corpus callosum that would have an impact on the dominance that was expressed through handedness; so, I did that. Frankly, I didn't find anything. I cut the largest fiber track in the central nervous system and the rats still learned the mazes well. They did all of the handedness studies, the same as before they had the corpus callosi transected. So, I really didn't find anything very important about this, but I did learn how to do research from him, and how to analyze data and so forth, and I'm very indebted to him for that experience. Of course, many years later, people who were a lot smarter than I was came along and did studies where they covered the eye of an animal, and after they had transected corpus callosum, showed that the rats were, essentially, learning with one half their brains and not the other half. But I wasn't smart enough to have done those studies.

TB: What did you do after you got your degree?

CS: Well, I left the University of New Mexico to enlist in the Air Force to do research. I had a master's degree in Psychology, and they were taking people directly into officer's training to do Psychological research. Well, something that I haven't mentioned was that while I was at the University of New Mexico, I had been involved in an activity that, at that time, was fairly novel;

I had played with a lot of African American musicians and it turned out that when I got to Albuquerque, it was segregated, and we could not eat together in the town with many of my black friends on campus, who were fellow graduate students. We could eat together on campus, but things were strictly segregated, and so, I began working with a group of people on getting an anti-segregation ordinance passed through the city, and we were successful in doing that. It was one of the first anti-segregation ordinances passes in the United States.

TB: What year was that?

CS: This would have been, in 1950, the first year I was in graduate school. We enlisted the aid of people from CORE and from other African American organizations to come there and we had civil disobedience. We would sit in the Rexall Drug Store at lunchtime, with 10 white individuals and 1 black, and if they wouldn't serve him, we wouldn't leave the scene and they would have to get the police to escort us out. And we created a lot of civil disobedience to bring attention to this. We also organized a national boycott of some of these stores, which were in Albuquerque, that were part of a chain. Some of the leaders of this organization that I was working with were known card carrying Communists and this was the McCarthy era. So, after I enlisted into the Air Force, they never called me up, because I found out, subsequently, that I was declared a security risk because of the fact that some of the people involved in this activity of getting this anti-segregation ordinance passed, were Communists. The Air Force, I presume, was afraid to call me up, because I had told them about this when I had my interviews, because I was not hiding anything and I was not and I never had been a Communist. But, I had worked with these people, and they were devoted to getting this anti-segregation ordinance through, and so was I. To make a very long story short, I had made no plans to go past my master's degree at that moment. I was going into the Air Force. By that time, I was married. I had a child and, suddenly, the Air Force didn't call me up, so I came back to the East Coast, which is where my family was, and I looked around for various kinds of jobs. I was very fortunate to get a job at Temple Medical School as an assistant instructor in Endocrine Biology. Well, I'll be honest, I didn't know very much about Endocrine Biology, but they needed someone, essentially, to be a glorified technician to do bioassay procedures and I was familiar with operative procedures in small animals because of my training and my master's degree. So, I went to work at Temple Medical School, in 1953, and I did all of what were the bioassays. We had to ovariectomize mice, and then, inject them with urine extracts from women

in which the estrogen had been extracted, and then, we would look for the presence of quantified epithelial cells in a vaginal smear, which was the indication that estrogen had been secreted. Anyway, I learned a lot about surgery in mouse. In the second year I was there, they had a visiting scientist from Israel, whose name was Bernhard Zondek; and Bernhard Zondek was the father of the Ascheim-Zondek pregnancy test, a very revered endocrinologist, who had moved from Germany to Israel, and he came to Temple to spend a year, teaching and so forth. Well, I was assigned to be his research assistant. I had a great deal of respect for Dr. Zondek; he was a superb clinician, but I will say, in all candor, that his science left something to be desired. One of the first things I was charged with doing was to do some research with rabbits with him. We would, again, be doing vaginal smears, looking for quantified epithelial cells; and I would get these things and I'd look at them under the microscope and I would say, oh, you see, there's some quantified epithelial cells. No, no, no, he would say. So, the next day, I'd bring them back and they were not labeled the same way and I would find that he changed his opinion. I don't know what was going wrong there, but, anyway, I got the privilege of working with him, and he said to me, ah, my boy, your future is assured, you worked with Bernhard Zondek. Well, about that time, Smith, Kline and French Laboratories, this was in Philadelphia, a little ways away from Temple Medical School, but on the same subway line, advertised for a research assistant, somebody with some training in Psychology. And I said, oh, I'm going to go look there, because that'll pay a lot better than Temple Medical School that was paying me \$212 a month, at the time; even then, in 1953, that was not a lot of money when you were married and had a child. So, I went to this job and it turned out that they wanted someone to be the assistant for a person by the name of Donald Bullock.

TB: What year was that?

CS: I can't tell you the exact year, but I worked at Temple for three years, this would have been 1956, approximately. Smith, Kline and French had, of course, obtained Thorazine (chlorpromazine) from Rhone-Poulanc, by then, and decided that this was such a blockbuster that they wanted to get someone who could screen for them other psychoactive agents that might have therapeutic benefit. They didn't know how to do this, and nobody knew how to do this, and this psychologist, Don Bullock, who was trained at Columbia University, and had been working at the University of Buffalo, but was paralyzed from the waist on down from polio, sold them the idea

of setting up a lab for him so that he could test their compounds in a variety of different animal types of procedures to see whether or not they had psychoactive properties.

TB: Wasn't Len Cook there at the time?

CS: Well, Len Cook was there. He was the head of the unit and he was using a classical avoidance procedure for screening of chlorpromazine like drugs, but we wanted to diversify from that, so Don Bullock needed an assistant. He was not hired, incidentally by Smith, Kline and French, because he was a Psychologist. They gave him a grant and a dog room in the back of the laboratory, and that's where I was hired to come and be his assistant. And I learned a great deal about, what we now call, Skinnerian psychology or operant conditioning, because that was Bullock's background and his training. I worked there for six months with him, and one Friday afternoon, he was summoned to a meeting and came back and said, "Bob, pack my things," and I said, "what do you mean?" And, he said, "Well, I've got to be out of here by 5:00 o'clock." Well, Don had a temper and would speak up at meetings about what he thought were stupid things that certain other people in the company were doing, and so, they decided that they were not going to renew his grant, and rather than keeping him around any longer, they said, he had to depart. So, here I'd had six month's crash training in operant conditioning and psychopharmacology, and my job, I thought, was over. So, I helped him pack up and helped him get all of his stuff out and to his car. He drove a car, a special car for someone who didn't have use of their legs, and he went on his way. Monday morning came. I came into the lab and I was sitting there and I wasn't doing anything. Then, E. J. Fellows, the director of Biological Sciences, came past and said "well what's going on; why aren't you working?" I said, "Well, you know, my boss got fired on Friday," and he said, "Well, you're in charge now." Well, Len Cook became very interested in the lab and we worked together. I had two consultants, Carl Prebome, who was, of course, a psychiatrist and had done a lot of research on brain function, and a psychologist, by the name of Charles Furster, who was an expert in operant conditioning and the principles of Skinnerian Psychology. So, for the next two years, I ran this lab, developed new behavioral assays, and screened compounds for Smith, Kline and French. And the company started to expand. We got technicians, and suddenly, the board of directors said, wait a minute, who is in charge of that program; and when they said, Mr. Schuster, they said, we've to get somebody in there, with a Ph.D. And, they decided to get a person with a doctorate, so that was Roger Kelleher, who is now deceased.

TB: When did you go back to school to get your Ph.D.?

CS: Well, I decided that I would go back to school at that point and get my doctorate. That year, Joe Brady had been a lecturer at Temple Medical School and gave his talk on the Executive Monkey, who had to make decisions all the time vs. a yoked control, which did not. The monkey, which had to make the decision, had to decide when to respond and when not to respond in order to avoid an electric shock. The monkey over here got the electric shocks if the executive monkey didn't behave properly, so they were equated in terms of shocks, but at that time, Joe reported that the executive monkey, who had to work 24 hours a day, doing all these things to avoid shock, developed ulcers, whereas the monkey, who received just as many shocks but didn't have to worry, didn't have a responsibility, didn't get ulcers. So, he was giving this lecture, I went to hear it, and when I told him that I wanted to go back to school, he said, well, do you know something about Psychopharmacology? And, I said, yes, and he said, well, we just got a grant at the University of Maryland to set up a Psychopharmacology laboratory. Why don't you come down there and I will pay you as an Instructor, because you know something and you can finish up your doctorate, at the same time, while helping us set up this lab? So, I went to the University of Maryland, then around 1958, and helped them set up one of the first academic Psychopharmacology labs. It was in an old abandoned Army building and it was a great place. There were a number of people there, who went on to do important things. Pete Grossman was a student there, who wrote a textbook on *Physiological Psychology*, later, and, many people went through this lab.

TB: Could you say something more about the work you did with Joe Brady?

CS: Well, Joe Brady was a fascinating guy and I'm sure, probably, will be interviewed for ACNP History, but Joe was, not only a Professor at the University of Maryland, he was also a Colonel in the Army over at Walter Reed Army Institute of Research. So, he could go back and forth between these two, and he had all of these draftees, who were Ph.D. psychologists, and he could get them assigned to Walter Reed. So, Walter Reed was a real hotbed of intellectual activity, and as I said before, he had this new Psychopharm laboratory over at the University of Maryland. Well, students at the University of Maryland could go over to Walter Reed and do things over there and vice versa. So, I went over to Walter Reed and there was an endocrinologist there by the name of Jim Mason, who had Rhesus monkeys, who were catheterized in their jugular veins in order to be able to remove blood repeatedly, so that he wouldn't have to go in and hassle with them and stress

them. He was trying to study hormones, and if he had to go in and wrestle with them to get a blood sample by venous puncture that would have stressed them and it might have changed the hormonal picture. So, he put these catheters in permanently, and the monkeys could run around their cage when they weren't in the study, but when they were in the study, he could put them into a chair, hook up a line from another room and had direct access to the venous blood supply of the monkey. And, I looked at this and I said, wait a minute, if he can take stuff out, I can put things in. My experience as a young jazz musician came back to me; those guys were always main-lining heroin and main-lining other drugs, putting them into their venous system. I was trained as an operant psychologist and I wondered whether or not if we put a drug into them, we could train an animal to perform some type of behavioral response in order to get that drug. And that began my career in drug abuse, a field that I've been with ever since, which is now almost 40 years. I was very lucky to have been in a situation where I could learn how to do this type of catheterization from Jim Mason and the people at Walter Reed. We got monkeys and we did the surgery over at Walter Reed, transferred them back over to the University of Maryland; and we began to study whether or not if we had a drug in a syringe and we made the syringe active if the animal pressed the lever, they would press the lever in order to get a drug. And it turned out that after a number of false starts and playing around, we were able to show that animals, Rhesus monkeys, would work for the same drugs that people abuse, and drugs that people found neutral, the monkeys found neutral, and drugs that people find aversive, the animals would actually learn to avoid getting an injection of those drugs. So, it appeared as if animals would find to be positively reinforcing the same drugs that people got in trouble with. At the same time as I made these discoveries, there were other people, who were also doing similar work. It was sort of a Zeitgeist phenomenon. Everything was coming together. The Department of Pharmacology at the University of Michigan, was run at the time, by a very famous pharmacologist, by the name of Maurice Seevers.

TB: Wasn't Seevers one of the early researchers in the drug abuse field?

CS: Dr. Seevers had been in the area of drug abuse research since the late 1920s and ran a department that had a heavy investment in drug abuse research. They had developed a similar technique to the one that we developed at the University of Maryland, and when I began first doing these studies, I had the audacity to write to Dr. Seevers and say, we want to find out whether or not animals will self-administer morphine. Could you please tell me what dose of the drug to use?

And, I love this, he wrote back and said, if you have to ask that question, you shouldn't be doing these studies. Go to the library; look it up. I mean, do your own work. Well, obviously, it was a naive question on my part. A couple of years later, after a meeting, at which he was present and I was giving a report on my research, he said to one of his young faculty members, go on and recruit that guy to come to the University of Michigan. I went to the University of Michigan, in 1962, after I got my PhD from Maryland, and began doing the type of research, this drug self-administration research, that I've been describing. I'd gotten a grant from NIMH, and I remember it was a grant for \$26,000.00 that paid my salary, for all the monkeys, paid for all the equipment, paid for all the research, and maybe, even a half technician. So, I went to the University of Michigan, in '62, as an assistant professor of Pharmacology. I was not a well-trained pharmacologist, at that point, but suddenly, I was in a Department of Pharmacology, and I had to be in charge of a lab and do heart/lung preparations, stop/flow kidney preparations, etc. Well, here I was a psychologist, with some training in Biology. I was not a pharmacologist, but over the next 6 or 7 years, I learned a lot about Pharmacology. The other thing that took place was that I had to attend every single pharmacology lecture. All the faculty in the department sat at the rear of the auditorium that the medical students were in, and after the lecture was over, all the faculty would go for coffee and we would discuss the pros and cons of the lecture that had been given that day. So, when it was my turn to lecture about psychoactive drugs, being a nonpharmacologist, I felt very much on the spot, and I probably worked much harder than many of the rest of them, because I was intimidated, but got by. About that time, I decided that there was no textbook in, what we call, Behavioral Pharmacology and one of my old friends from the University of Maryland, who had gone to the University of Minnesota, and I got together and we wrote the first textbook in behavioral pharmacology, which was Thompson and Schuster's *Textbook of Behavioral Pharmacology*. It did pretty well; and I'm still very, very proud of that book, because I think it was important, in terms of helping to get people with an interest in behavior to be aware of the fact that you could learn a lot about *behavior* from pharmacological probes and you could learn a lot about how drugs affect behavior by using sound and sophisticated behavioral procedures and that's what we stressed in that textbook.

TB: What year was your textbook published?

CS: The textbook was published in the early 1960's. I think it was about 1963.

TB: 1963.

CS: It was probably a little later. I'm sorry. It would have been '64 or '65. I stayed at the University of Michigan and, as I said, learned a lot about pharmacology, while I continued my research in drug self-administration. I worked there with Jim Woods, who is, of course, a member of ACNP, and one of the foremost psychopharmacologists working in the opiate pharmacology area. Jim was originally my technician there, and he had finished everything, but hadn't yet written up his dissertation. So, I kept bugging him to do it, and he didn't get around to doing it until I announced that I was going to leave. I was going to leave, because a guy by the name of Jerome Jaffe, one of a really smart young psychiatrists, pharmacologist, had been recruited by the University of Chicago, in the state of Illinois, to set up the first monomodality drug abuse treatment program in the US. It was called the Illinois Drug Abuse Program. It was centered at the University of Chicago but had clinics and facilities all over the state. Well, for some reason, he was intrigued with the research I did, and although I did monkey research and rat research and pigeon research, he said, come on over and become associate administrator and do human research in the area of drug abuse. I said, wow, that's neat. That's a real challenge.

TB: What year was that?

CS: I went to the University of Chicago in about 1967 or '68. I say, '67 or '68, because I stayed half time at Michigan for a year and half time at the University of Chicago, because I had graduate students, who were finishing up at the University of Michigan. Finally, I got over there and was in the Department of Psychiatry and Pharmacology at the University of Chicago. At that time, the Chairman of that department was Danny Freedman, who was just an absolute delight and a source of great intellectual stimulation to me and everyone in the department. When I got over there, I started to do human research. But I also hungered to set up an animal research laboratory, as well, because there were many questions that I wanted to ask that I couldn't answer in humans because of ethical and considerations. So, I wanted to have a situation in which I could do human research and animal research, as well. And, so, I was fortunate to be able to set up a large animal laboratory, while at the same time, I was able to conduct human research in the clinics that we had for the Illinois Drug Abuse Program. We did some of the first studies with a maintenance medication for the treatment of opiate addiction, back then.

TB: What was the drug?

CS: It was LAAM, or L- α -acetyl methadol. Jerry Jaffe got a call from a psychiatrist on the West Coast, who said, you know, I've got a bottle of this stuff, called L- α -acetyl methadol, and Fraser had studied this at the Addiction Research Center in Lexington, Kentucky, years before, and shown that it has the action of a very long acting opiate. It was a Merck compound and originally, when they put it out for the treatment of cancer pain, they ran into some overdosage problem, because they didn't realize that one dose would last for two days. So, they gave cumulative doses and dropped the drug, after they ran into a few deaths. Well, we got this bottle of L- α -acetyl methadol, which at this point was 15 years old. So, Jerry said, hey, we should try this on a couple of methadone patients, and if it's really long acting, maybe we can use it instead of methadone and we will only have to dose them every couple of days, instead of every day. So, the first thing we had to do was to decide whether this drug in this bottle was still good. So, I went to Christian Ikizdere, who was the chemist for the IDAP program, and he said, well give me some. He ran it on thin layer of chromatography, and it came out with one spot; so, he said, okay, it is fine for humans. Now, that one spot could have been something other than LAAM, but we said, okay, it's going to be okay. Well, we didn't know exactly what dose, but we were conservative, so I called up the local methadone clinic and I talked to Ed Washington, who was the person who ran it, and I said, send me over 4 people, who are willing participate in an experiment, and he sent over 4 people. Well, I thought to myself, I will explain to them what we were going to do, that we are going to give them a new medication that we thought might be as good as methadone, but it might last longer, and they said, okay, and they will say we'll participate in this. Now, you have to bear in mind, there was no human investigations committee at the time; there was nothing about passing any ethics test, etc. We knew very little about this compound, but we knew that it had been given to humans, and we knew the right dose, approximately. But, I said to myself, okay, let's not do this quite yet. In our methadone clinics, we gave out methadone in different flavored Kool-Aid. We had clinics that were labeled like Rooting Tooting Raspberry Clinic, because that was the flavor of Kool-Aid. We had Lefty Lemon. That was another clinic. So, these guys came from a Raspberry Clinic and I decided to give them their methadone that day, but I changed it to Lefty Lemon, not in their usual Raspberry, but I didn't tell them that. All I can say is that I am very fortunate that I did not give them LAAM, because if I had, we wouldn't have L- α -acetyl methadol on the market today, because within 30 minutes after I gave them their regular dose of methadone,

but in a different vehicle, a lot of them had hysterical paralysis in the legs. I didn't know it was hysterical paralysis. They couldn't walk. One developed a panic state and two of them were fine. Well, if I had given them the new medication at that point, I can assure you, I would have never given anybody else this, because what was essentially a placebo intervention, the thought that they had received new medication instead of methadone was sufficient to produce these responses. So, I called up Ed Washington and I said, hey, you know, don't send over any of those crazy people that are going to react to this kind of thing; I need some stable people. So, he sent over some more people and we began to do research, then, with L- α -acetyl methadol.

TB: When did this happen? Was this in the '70s?

CS: That was in the early 1970's and LAAM was only marketed, I believe, in 1993, which tells you something about drug development, when there's not a large market for it, as there isn't for treatment for the heroin addiction. So, it was about that time that I was admitted into the American College of Neuropsychopharmacology. Let me go back just a moment to reflect about my first trip to ACNP.

TB: When was that?

CS: That was actually back when I was at the University of Michigan, in the '60s, and I was coming down, at that point, to a meeting that was being held in Puerto Rico, but not at the Caribe Hilton where most of the meetings are held that I've gone to since then, but it was in another, hotel, at the Sheraton, probably. I had never been to ACNP before, and I was coming to give a talk on opiate pharmacology. My co-author was a very eminent young guy, by the name Julian Burreal, who was an M.D., Ph.D. pharmacologist, and an absolutely delightful scholar. He was the co-author, but he didn't get to go on the trip. They would only pay for one of us, so I boarded the plane with my slides and with my paper. I got to Miami and had to transfer planes to go to Puerto Rico, and after I sat down in the seat, the gentleman next to me started talking to me and he asked, what are you going to Puerto Rico for? And, when I told him, he said, well, that's where I am going. And, I told him, fantastic. He said, my name is Bill Krivoy, and I do opiate pharmacology research. And, I said, oh, well, I'm giving a paper on opiate pharmacology. He said, I guess you've reviewed all my work; and I thought, no, I haven't, no, what am I getting myself in for here? Well, it turned out that Dr. Krivoy had done some excellent work on spinal function with opiates and spinal reflexes, but that was not the thrust of my talk. But I was scared to death, because, here I

am going to this meeting with all these preeminent people, and the guy sitting next to me says, you must be quoting all of my work, and his name is not in the list of my references. Well, I got there and I gave the talk and got through it and he was in the audience, but he didn't say anything, but it was my first experience. And, one of the things that for me was the most impressive about the meeting, was the fact that there were not only pharmacological researchers such as I was and people with an interest in psychology, but there were clinicians. There was a complete mix of people, and so, they asked questions that were very different than if I'd gone to an ASPET meeting, because they asked about clinical relevance for things that I was doing in animals. And I think that's one of the things that turned me on about ACNP from the very start; the mixture of disciplines, which were brought together, and the kind of people that one was privileged to meet, so you got asked questions that you wouldn't get asked, ordinarily. And, I wasn't necessarily able to answer them, but I went home thinking about them, and they may have become some of the impetus for the next research that I did.

TB: At the University of Chicago?

CS: Well, let me just say that I continued, at the University of Chicago to do research. I actually left the Illinois Drug Abuse Program for a couple of reasons. I was interested in treatment and treatment research, but at that time, there was some real constraints about being able to do things within the context of a state managed program, in terms of changing things or doing studies where you would have a control group. When Jerry Jaffe and I first started the program, we had this, what now is, obviously, a very naive kind of concept that we were going to bring heroin addicts in, because the problem that they were interested in at that point was heroin addiction, and we were going to randomly assign them to, either a therapeutic community, to methadone, to detoxification followed by after care counseling, or to a waiting list control group. Well, the first thing that happened, I got the names of the first people and started to do this, was that my secretary said, I won't type this list, because you've got a waiting list control group in there, and it's unethical; you can't let just people, who want to come into treatment, stay on the street for a while. And, I can say, we really have never had a control group of that sort in the area of methadone maintenance. Although, there's no question, through a variety of other studies, we've established the efficacy of methadone, but without having a treatment control. So, we didn't have that. The next thing we discovered, you can't randomly assign people to grossly different kinds of therapies.

Fifty five year old heroin addicts, when we assigned them to a therapeutic community and they were told, you're going to have to grow up all over again; we're going to reduce you to being an infant, and you're going to have to learn responsibility and grow up, came back to us, saying, are you nuts if you think I'm going to go and spend a year in that place? No. It was not appropriate for these older heroin addicts, and so, we gradually learned that we could not randomly assign people to all of these diverse kinds of areas, but we did begin to do a few studies. I decided that I would, rather than doing treatment research at that time, I would rather leave the IDAP program and go into laboratory research in, both animals and humans. And so, we founded the Drug Abuse Research Center at the University of Chicago and we were able to get NIMH funding, and then, subsequently, NIDA funding for supporting this. And, in the laboratory, at that time, were some important people, who are members of ACNP, one of whom also happens to be my wife, Dr. Chris- Ellen Johanson, who was a graduate student at the University of Chicago and did research in the primate laboratory, there. Dr. Marian Fischman, also a Fellow in this Society, who first did animal research, looking at the neurotoxicity of methamphetamine, a topic that we're going to discuss here in 1999, tomorrow night. Many, many other people were at the University of Chicago, but those are just two of the people that popped to mind. Both of them went from doing primate research to doing human research. Dr. Fischman started doing human research with me at the University of Chicago at a time when cocaine started to be a drug that came to prominence in the United States. When we looked at the literature and saw that there had really been no human studies done, essentially since Sigmund Freud had done studies using himself as experimental subject, we decided that it might be time for us to do some human research with cocaine. Well, to say that we ran into some obstacles is to put it a little bit mildly.

TB: What kind of obstacles?

CS: The first thing was, the FDA said, well, if you're going to use people to do human cocaine research, you have to screen them and establish that they've been using cocaine three to four times a day, every day, for the past three months. Well, that was not the way cocaine was used at that time. It was used in binges and quit. So, we, then, had to do a small epidemiological study to show the binge pattern of cocaine use, rather than the fact that it was like heroin taken regularly every day. We came back to the FDA and were able to show them that this was not the pattern of use of cocaine and that we needed to bring people in who used it in a binge fashion. There was

also great concern because cocaine is not only a psychoactive agent, but also has local anesthetic properties, that it would cause a conduction block in the heart, and many of my M.D. colleagues and many of the fathers of drug abuse research said, oh boy, you're really stepping on dangerous ground to use cocaine in humans, because it may ice them, that is, cause this conduction block in the heart. And, I said to them, well, you know, I've been doing Rhesus monkey research, now for 15 years with cocaine, and I've never seen an untoward death that was not dose related. I told them that I've never seen anything at moderate doses, and that we're very conservative and we will be not putting anyone at great risk. We, obviously, got cardiologists to be involved in this research and Dr. Fischman and I began to do this. The first thing was, we had to get the Provost to sign off on the grant, and I remember him saying this to me, "Schuster, if you hurt somebody with this research, your career is ended." And I said "well, you know, I think it is very vitally important research." I think that the animal research that we've done for the past number of years indicates we can do this, and I can say that we've been doing cocaine research for some time now, and we have never run into any really adverse events that were life threatening to individuals. So, my only point here is that we began to do, what I think was very important human laboratory research there, and that is something that I continue to do today.

TB: When did you move to NIDA?

CS: In 1986, at sort of the peak of my career at the University of Chicago, I got a call from some people in the Federal Government, saying that there was position open, the Directorship of the National Institute on Drug Abuse, and I said, are you kidding? Everybody knows that first of all, I was declared a security risk back in the McCarthy era, everybody knows that I was a young jazz musician because I've openly discussed this, and that I'd smoked marijuana, and above all of these things, I'm a known card carrying Democrat, and this is a Republican administration. They said, well, come down and interview for this, anyway. So, I went down to Washington and I interviewed for the job, and I can tell you, there was a member of the Parents movement there. The Parents movement was very active at that time and continues to be active in terms of Drug Abuse Prevention, and one of the people, on that committee was Shirley Colletti from Florida. She started prevention programs, treatment programs, and has done a dynamite job down there. She was on this committee and when I walked out, for whatever reason, she said, that's the person that we want to be the director of NIDA, and she was persuasive. And so, I left my position at the

University of Chicago, in 1986, and went to the National Institute on Drug Abuse as the Director of the Institute. I knew NIDA a little bit, because I'd been on study sections and I had been there as a consultant to them on many occasions, but there's nothing like walking into the director's office and realizing that, suddenly, you're in control, so to speak. I found out how little control you have after a while; but, theoretically, you're in control of the major institution in the world that provided funding and direction for drug abuse research. At the time I went there, the budget was 85 million dollars a year and that was an astronomical amount of money, but I was there a short while and things began to happen. A basketball player at the University of Maryland died of an over-dosage.

TB: Who was the player?

CS: His name was Len Bias and he hit the newspapers. He had been signed to the professional NBA at an astronomical amount of money, because he was an incredible basketball player. Obviously, clearly a healthy physical specimen and he had overdosed on cocaine and died and newspaper headlines went out, like all over the country, about this. Congress just became possessed with the idea of cocaine and the horror that it presented to us. At the same time, it was being established that HIV infection in AIDS was being transmitted by drug abusers, who were sharing needles, particularly in New York City where the rates of HIV infection were escalating. So, in the next six years that I was at the National Institute on Drug Abuse, the budget went from 85 million to over 400 million, because of the incredible public clamor for doing something about the problem of cocaine addiction and doing something about the problem of the spread of HIV infection amongst those who are using illicit drugs, particularly by the IV route. It was an incredible experience to be in Washington at that period of time, and to have a role in attempting to develop a research base for trying to help those, who were out in the community trying to deal with the reality of these problems, namely cocaine use and spread of HIV infection through dirty needles. I can say that there were a variety of very positive things that happened, in terms of the government, at that time. Now, you have to understand that as an institute director, I could not lobby Congress for money for my institute. That was against the rules. You can't do that. You could be dismissed for lobbying Congress, directly, for money. And I was breaking the rules. What happened was that I was told that a person named Mr. Conti wanted to put about a 10 to 15 million dollar proposal into the NIDA, but he wanted his name on it, and I said, fine. I was, that

day, in New York City and listening to the AIDS statistics. And by the time I got back to my hotel about 5:30, I was really depressed, because HIV infection was going up, up, up, it was getting up to thirty-five to forty percent of the intravenous drug using population in New York City, and there was no solution in sight. The thought of this spreading across the United States was just horrific, so I could, with a great deal of passion and emotion, call and say to a congressman, that we need 10 to 15 million dollars to establish a Medication Development Division in order to develop new medications for the treatment of heroin addiction, because if we don't have options, besides methadone, I'm afraid we will not be able to totally cope with the problem of HIV infection and its spread amongst heroin users.

TB: How did he respond?

CS: He said, well, how much do you think that will cost? And, I said, around 10 to 15 million dollars. And, what you find out in the government is once you get a named area of research by Congress, that's sort of like a bucket or a basket into which money can then be put in the subsequent years. And, of course, the Medication Development Division at NIDA has grown and has been responsible for a number of activities over the years, and I'm very glad that I selected that particular area to be the emphasis for Mr. Conti. I can say that, and, here I will be very blunt, because I want it to be recorded for history, that there was a great deal of animosity towards drug abusers in many aspects of the government during the Reagan administration. During that time, I had the privilege of going around the world on Air Force One, spending three weeks with Attorney General Meese, Frank Lawn, who was head of the Drug Enforcement Agency, and the Governor of Oklahoma, Frank Keating. We all went around the world together on Air Force One to the drug producing countries, and they went off to see the police and the people charged with supply reduction, and I went to the demand reduction people in those countries. Many of the people on the plane, who accompanied them, in talking to them about drug abusers, referred to them in extremely derogatory terms. Some even espoused the principle that maybe it was modern day evolution to let them have all the drugs they wanted, so they just overdosed and died. AIDS was God's way of punishing homosexuals and drug abusers. This was common banter and it was a very difficult time for me to be on that plane, because there was not much point in trying to argue. I argued a little bit rationally once with someone who said that drugs were simply modern day evolution; let those junkies overdose and die. I said, well, you know, there's only one problem.

They usually don't overdose until after they reproduce, so it is not going to work. As I say, it was the attitude toward drug abusers. Then, Leslie Clarke, the director of CSEP had the major initiative to try to overcome this stigmatization, because when people are stigmatized this way, they won't come in for treatment until they are really desperate, in other words, until it's almost too late to do things that we could have done much more effectively, years earlier.

TB: Until when did you stay with NIDA?

CS: In 1992, I left the directorship of the National Institute on Drug Abuse, for personal reasons, and there was a little bit of a problem, because my colleague and wife, Dr. Johanson, had been selected, after two nationwide searches, to be a Branch Chief in the Intramural program that I directed, and that was found to be okay by many people, until it reached certain high level positions, and they felt that that was unethical. And, I said, well, if she cannot take this position, then, I no longer will be the Director of the National Institute on Drug Abuse, so I resigned. She took the position, and I joined her at the Addiction Research Center, as a Senior Research Fellow there, and we stayed there for 3 years, until Dr. Tommy Hudeyat at Wayne State University School of Medicine offered us a position that we couldn't refuse. So, we've gone to Wayne State University in Detroit, where we have laboratories, and direct a number of drug abuse treatment programs and research. Although, I'm technically more than old enough to retire, I have no intention of doing it in the foreseeable future, and I'm as excited about everything I'm doing today, as I was about anything I've done in my life. We're doing a lot of research with behavior in conjunction with pharmacological interventions for the treatment of heroin addiction and cocaine addiction; doing a lot of work on smoking cessation problems and in the development of new medications to assist people in that area. And we've done some recent studies on cocaine addiction in individuals, who meet the criteria for adult ADHD, or ADD, and so, we've got a lot of interesting things going there. I'm very excited about the research and hope to be able to continue to contribute to it for some years to come.

TB: You did research in many areas within the field of addiction. What would you consider your most important contribution?

CS: Well, I would say a couple of things. I think we advanced the field of drug abuse immensely when we were able to show that organisms, other than humans, would self-administer drugs, and that they would do so in a way that was lawful and, I mean, lawful from the pharmacological

viewpoint, that you couldn't attribute this to many of the psychological theories that had surrounded drugs of abuse in the past. I can remember that there was one analyst, and I don't remember the name, who wrote that individuals became addicted to heroin because it decreased their sex drive, and if they had any latent homosexual tendencies for which their super-ego produced great guilt, they could resolve this by taking heroin. Well, I looked at my monkeys and I thought we should look at some other reasons. Now, I'm not saying that there aren't psychological factors, co-morbidities, and a variety of other things that influence the propensity of people to take drugs. There's a variety of ways in which mood disorders that could be genetically determined, might influence the propensity to take drugs. But, I would still argue that I have rarely, if ever, seen a Rhesus monkey that will not self-administer cocaine after they've had some experience with it, and that's true for most of the rat strains that have been looked at. I think that organisms, which ingested these things and found them immediately reinforcing, were those who survived; so, we laid down these tracks in the brain, in the mesolimbic subcortical dopaminergic pathways, and others. So, those were laid down via evolutionary mechanisms, and they're responsible for the fact that drugs of abuse, which have the capacity to interact with those brain systems, are so insidious because they can directly produce the kind of experience, which many of us get from other activities which we find reinforcing.

TB: So, you recognized that drugs of abuse could produce the kind of experience that we find reinforcing.

CS: Well, I've been lucky. And I make no bones about it. My early drug abuse career gave me this interest in drug abuse.

TB: It seems that your experiences at Walter Reed, and also at SKF, had a major impact on your professional development.

CS: Now, let me talk a little bit about Smith, Kline and French. That, clearly, was one of the turning points in my own career, because prior to that time, I had been interested in the brain, but I didn't know anything about pharmacology. I was fortunate to come in at the time of the major revolution; chlorpromazine was introduced onto the market in the United States, at a time when American psychiatry was largely dominated by psychoanalytic thinking and the idea of biological psychiatry was rather foreign. Also, the the notion that medication might be useful was foreign to the thinking of most psychiatrists. So, Smith, Kline and French spent a year before they actually

took the drug onto the market, but within a few months after they did, train loads were going out to state mental institutions all around the country. So, this was very, very exciting.

TB: Didn't you develop several procedures while with SKF to study how chlorpromazine affects behavior?

CS: Yes, what happened was that there had been findings that chlorpromazine would block the avoidance behavior of rats, in doses that did not affect their escape latency to electric shock or other adverse stimulation. That was all that was used. When I came to Smith, Kline and French, we developed a variety of different kinds of procedures for studying how drugs might affect behavior, including what was called the Conditioned Emotional Response, where animals that were working to obtain food, periodically would be given a warning stimulus that would last for five minutes, but at the end of that five minutes, no matter what they did, they were going to get a shock. Between the warning signal and the shock, animals would show great autonomic activity. Rats would urinate and defecate and they would stop responding for food, because they were, essentially, in a state of fear during this period of time. So, we were looking for agents that might overcome some of these autonomic changes. At the same time, we were concerned that drugs like chlorpromazine might have toxic effects on cognitive processes, so we had monkeys, who were being forced to learn new things all the time in order to see whether or not chlorpromazine would interfere with new learning.

TB: You have mentioned it before that you collaborated with Len Cook, while at SKF.

CS: Yes, Len Cook was in charge of the screening for new psychoactive medications. Dr. David Tedeschi was also there involved with screening. The laboratory that I was involved with was a laboratory that was to develop new techniques. That if they showed anything interesting, could then be put into the routine screening laboratories that they headed up. Dr. Cook was my boss and I learned a great deal from him. One of the fortunate things there was that they encouraged those of us, who didn't have a background in pharmacology, to take an extension course in pharmacology, which was run by the University of Chicago, and Dr. Kelsey of thalidomide fame, was the instructor for that course. And the pharmacologists at Smith, Kline and French would then give us lectures at work, which was really marvelous, and it was a great opportunity for me to learn, and I contributed by bringing my skills as a psychologist to them and they taught me a little bit about pharmacology.

TB: Then, in the mid-1960s, you published the first textbook on *Behavioral Pharmacology*. Could you tell us something about that important book? Have you considered publishing a revised, second edition?

CS: The *Behavioral Pharmacology* textbook, which Dr. Thompson and I wrote, was widely used in psychology departments and since behavioral pharmacology suddenly burst on the field, having a textbook at that time was very helpful to many, many people. I don't know how to say this, but I still run into people who say to me, my first introduction in this area was using your textbook when I was an undergraduate at this school back in the '60s. Dr. Thompson and I, we'd been together at the University of Maryland, but we separated. I went, first, to the University of Michigan and, then, to the University of Chicago and he went to the University of Minnesota. Although, we talked about revising this book, we never did it. It was never revised, but I will tell you that the opening chapters of that book, I would write again today.

TB: Could you tell us something about your activities in the ACNP?

CS: Sure. The American College of Neuropsychopharmacology has been very important to me and I hope that in, at least some small ways, I've helped to contribute to its activities. I have been the Chair of the Credentials Committee on, at least, two occasions, and have participated in many, many of the meetings in a variety of ways, both as member of committees, a part of the infrastructure of ACNP, as well, and probably in two thirds of the meetings that I've come to, and I've come to most every single one of them, I have made a presentation. And many students and colleagues, whom I've brought to the College, have also made presentations. So, I would say I have continued to be active in the College and look forward to continuing to be active into the future.

TB: On this note we should conclude this interview. I would like to thank you for sharing all this information with us.

CS: You're welcome. Thank you.

58. ERIC M. SHOOTER

TB: This will be an interview with Dr. Eric Shooter⁶⁰ for the Archives of the American College of Neuropsychopharmacology. It is December 9, 2002. We are at the Annual Meeting of the College in San Juan, Puerto Rico. I'm Thomas Ban. We should start from beginning. When and where were you born? Tell us something about your education and how you got involved with neuropsychopharmacology.

ES: I was born in a small village north of Nottingham, in England that was part of the original Sherwood Forest. My family jokes that we got our name from our ancestors, who were the shooters in the forest, clearly on the side of Robin Hood and not the sheriff of Nottingham. But, my family moved after about two months and my father, who was a mining engineer, became an inspector of mines in the mining district, which encompassed the counties of Derbyshire, Nottinghamshire, and Staffordshire. The town in which we were situated, Burton-on-Trent, was outside the mining area with easy access to all three counties. It was a major brewing town, where beer had been brewed since William the Conqueror, using water from the local wells. I lived there until I was eighteen and left for Cambridge, and I had a very pleasant childhood. I had one brother, Kenneth, older by eighteen months, so there was always a companion around, for better or for worse. My parents were very loving, but reasonably strict. I went to state schools, first from five till eight or nine, then to an intermediate school, and from there, I managed to win a scholarship to the local grammar school, which had been founded, in 1521. It was a relatively small school with three hundred pupils, ranged in the age from ten to eighteen. It had a good teaching staff, strict but relatively pleasant, a very encouraging atmosphere, and a nice place to thrive. We studied the usual set of subjects and played a lot of sports including, cricket, rugby, running, and tennis. When it came time to specialize, it was easy for me to choose the topics, science, math, physics, and chemistry. In the small amount of science I'd taken in the first four years, I came to enjoy its

⁶⁰ Eric Shooter was born in Mansfield, England, in 1924. He received his Ph.D. after studies at the Department of Colloid Science in Cambridge and at the Royal Institution in London, England. After post-doctoral training at the Department of Chemistry at the University of Wisconsin, he accepted a position as scientist at the Brewing Industry Research Foundation in the United Kingdom, and then, joined the faculty of the department of Biochemistry at the University College of London. After a sabbatical in the Department of Biochemistry at Stanford, California, he subsequently left University College London to return to the United States to join the faculty of the Department of Genetics at Stanford. He eventually became the founding chair of the Department of Neurobiology in the Stanford University School of Medicine. He was interviewed in San Juan, Puerto Rico on December 9, 2002.

logic. You could ask a question and get a reasonably straightforward answer, without too many permutations. In those two years of specialization, I went through to the second level of examinations, the higher school certificate, and qualified for college at age 16. I had a headmaster who was a superb person with a number of great attributes. He was determined to get more of his students from our school, the Burtonon-Trent Grammar School, into Cambridge. He'd just come from a senior position in Cambridge and knew how to do this. He also insisted that nobody should attempt to go to college before the age of eighteen, so he suggested I stay around for another two years, in the Sixth Form retaking and expanding the same subjects. It was very good advice; the third year was with other boys doing the same thing, the fourth year by myself. We were given textbooks of *Experimental Physics* and *Experimental Chemistry* and allowed to work our way through them, which I did with great abandon and pleasure. I recall when I managed to accidentally light the hydrogen jet and blow the apparatus up. It disappeared through the roof, and there was a little bill to pay for the repair. Aside from that, I learned a great deal about experimental physics and chemistry, which helped me enormously when I finally went to Cambridge.

TB: What year did you go to Cambridge?

ES: I took the exam for Cambridge, in the year 1941, passed, and was admitted to Gonville and Caius College, in 1942. Being wartime, the decision whether I went to college, or not was made by a National Board.

TB: What did you do at Cambridge?

ES: I had three years at Cambridge, studying mathematics, physics, and chemistry and an extra subject of mineralogy. Although many of the Fellows of the colleges had gone off to war, the teaching was still at a very high level, and we benefited from the usual Cambridge system, having a weekly tutorial, one on one or two, with experts in my chosen subjects. I found mineralogy much to my liking, the characterization and study of mineral crystals and their analysis by x-ray crystallography. Given my choice, I would have become a mineralogist, but at the end of two years, the British government decided that chemistry would be an important subject after the war. So, they told a group of us that if we wanted to study chemistry for a third year and specialize, we could stay on. There were twelve or thirteen of us who opted for that. I completed the third year successfully, in the summer of 1945, as the war was ending, and was able to immediately stay on

in Cambridge as a graduate student in the Department of Colloid Science, a department committed to the study of the chemistry of large molecules.

TB: Chemistry of large molecules, could you elaborate?

ES: Large molecules are the naturally occurring polymers and proteins like collagen or the plant polymers. It was a topic that was to become increasingly important with the manufacture of man-made polymers. Nylon came into being, about 1947, during my graduate work, so the subject had enormous importance for understanding the properties, chemical structures, and the characteristics of these compounds. My supervisor, Paley Johnson, had originally been going to get me to work on rubber as one of the important polymers, until he found a postdoctoral fellow to do that and thought I would enjoy working on the proteins of the groundnut (peanut) instead. It was known that you could extract proteins from peanuts and spin them into a fine fiber, which was quite elastic and stable, suggesting the possibility of making cloth and garments out of peanut protein. Before that got very far, however, it was superseded by nylon. Interestingly though, the British government thought it could help England, where they were still rationing and countries in West Africa nutritionally, if they grew peanuts. So they set out to do this on a large scale in West Africa. Curiously, they'd never done a pilot study, so when they started largescale production, they found there were many animals and insects in Africa, who enjoyed these peanuts, and they only collected a few pounds from many thousands of acres planted. Anyway, I was willing to study peanut proteins because it meant I would learn two of the methods available at this time for studying polymer structure, ultracentrifugation and electrophoresis. These methods required big complicated pieces of equipment, in which the movement of proteins in solution, under a centrifugal or electrical field, was followed with a schlieren optical system. The first year was spent in the Department of Colloid Science, in Cambridge, but the Head of the Department then decided to move to take up Directorship of the Royal Institution, in London, and most of the department members decided to move with him, including myself. The Royal Institution has a long and distinguished history in British Science, being the place where Faraday, for example, made all his important and original discoveries. It has a rich scientific atmosphere, including a magnificent library, and is renowned over the years for its Friday evening discourses, given to a lay audience by distinguished scientists with an emphasis on scientific demonstrations. The experimental equipment of many of the previous directors is displayed in the Institution, as well

as plaques to denote their workplace, such as the plaque in the floor of the laboratory where Faraday kept his frogs. One of the more recent visitors to the Institution was Madame Curie, who left her own imprint in the form of traces of radium in the drains. This was not discovered for many years, until Sir Lawrence Bragg came from Cambridge, in the early 1950s, to fill the Faraday Chair and restart crystallography research in the Institution. All his X-ray film was fogged up before he started his experiments and the culprit was the radium in the drains.

TB: When did you get your Ph.D.?

ES: I completed my Ph.D., in 1949, and wrote a thesis describing the characterization of the major peanut proteins. Altogether, it was an extraordinary few years where I was allowed to work essentially independently. At the end, I decided this was an area of research that I would like to take further, and so, I applied for and received a one-year post-doctoral fellowship in the Department of Chemistry at the University of Wisconsin, a world-renowned center for macromolecular research.

TB: This was in...?

ES: This was 1949. In November, my wife and I left the UK for America, on what was our honeymoon. We arrived in New York with ten dollars, each in our pockets, the maximum amount the British government would allow us to export. Ten dollars, I expect, is about a hundred dollars now, so it wasn't quite as bad as it sounds. You can do these things when you're twenty-four! I'll never forget the welcome we got, when we finally arrived in Madison. My major professor, Jack Williams, came to the railway station to meet us with his car and said, "Hello, Eric and Elaine. I'm Jack and you will call me Jack." We couldn't do that. That was much too much of a transition. It was a terrific year, working under Jack Williams who was a very distinguished professor of chemistry. He was one of the few members of the National Academy at the University of Wisconsin. There was also a very bright and energetic young assistant professor, Bob Alberty, in the department, who had come from the University of Nebraska, and Bob was very much into the theory of the sedimentation and electrophoresis of proteins. I learned a lot from both of them. I worked on the separation of serum from proteins and found you could identify five groups. One of the groups was the immunoglobulins, which were beginning to get a lot of attention.

TB: What did you do after the year in Wisconsin?

ES: I returned to England, in the middle of December 1950, to take up a position I'd accepted before I went to America, as a scientist at the Brewing Industry Research Foundation. There was a large amount of money in their research fund and they decided to emulate the Carlsberg Laboratories, in Denmark. The Carlsberg Laboratories had been deeded into a foundation. All the profits from the brewery went into two research laboratories, the physiology and microbiology laboratories. The idea was to do basic research on the biochemical and microbiological process of brewing. The goal was not principally for brewing, but to benefit mankind, and they became very distinguished, particularly, the physiology laboratory. They did very early work on protein structure using micro methods of analysis. So this is how the Brewing Industry Foundation in England got started. A number of us were recruited. I went there to characterize barley and malt proteins, using the two methodologies of centrifugation and electrophoresis.

TB: From the Brewing Industry Research Foundation, you moved to the University College of London?

ES: I was fortunate to get a job as lecturer in biochemistry in a distinguished department of Biochemistry, at the University College of London, the only department in the University of London that was then teaching biochemistry at the Master's degree level. For me, it was an eye opener and a very good way to learn how to teach, both the experimental procedures and formal didactic lectures. We taught a course in experimental biochemistry, where we devised the experiments and then stayed with the students from nine in the morning until five in the afternoon, mentoring and tutoring them on the experimental procedures. It made teaching much easier and I learned a lesson for later; what it might be like to teach a class of several hundred medical students, the basic aspects of biochemistry, and to enjoy it, rather than have it be a chore. Later on, I did get to do research. In the late 1950's, I came to know an anthropologist at the college, who was working in Africa, studying the genetics of blood groups in different populations, and he would bring back samples of blood, from which we could isolate the major red cell protein, hemoglobin. Very shortly after that, Pauling showed by electrophoresis that sickle cell hemoglobin was different from normal hemoglobin, and Vernon Ingram showed that there was a single amino acid substitution, which changed normal human hemoglobin into sickle cell hemoglobin. This opened up the whole field of hemoglobin genetics, the study of a variety of different hemoglobins, and how a single amino acid substitution changed the properties of proteins in such a way that it gave

rise to a very definable disease. In the case of sickle cell hemoglobin, that single change made the protein sticky, so unlike normal hemoglobin, which can change from oxygenated to deoxygenated hemoglobin with no change in solubility, deoxygenated sickle cell hemoglobin aggregates into sickle cell shapes that have great difficulty going around in the circulation, causing the concurrent symptoms of the disease. This was the start of biochemical genetics, in terms of protein structure. My colleague was a brilliant hematologist, Ernie Huehns, in the Hospital at University College. He was able to collect from the various immigrant populations in London, different hemoglobins that we could classify and characterize. We were responsible for discovering hemoglobin G and for characterizing an α chain variant. We also, with A.B. Raper, proved that two genes, one for the α -chains and one for the β -chains, controlled the synthesis of hemoglobin. Then, towards the end of the 1950s, I thought I should learn something about this upcoming subject of DNA and went on a sabbatical to join Buzz Baldwin in the Department of Biochemistry, at Stanford University.

TB: So we are now at the end of the 1950s.

ES: The medical school had just moved from San Francisco and built a new hospital. It provided the opportunity to bring together a new cadre of incredible chairmen in the basic and clinical sciences; David Hamburg, for example, who was appointed Chair of Psychiatry, was one of the first biological psychiatrists, in the early 1960s. Norman Kretchmer was Chair of Pediatrics, and Henry Kaplan, Chair of Radiology; on the basic science side, Avram Goldstein in Pharmacology, Joshua Lederberg in Genetics, and Arthur Kornberg in Biochemistry. The whole place was humming with intellectual vigor and I could not have chosen a better place to visit. By studying the melting behavior of a hybrid DNA molecule, in which one strand was labeled with bromine, Buzz Baldwin and I were able to show that the replicating unit of DNA is the single strand. Although this result seemed obvious from the structure of the Watson-Crick helix, it had not been formally proven.

TB: What did you do after your sabbatical at Stanford?

ES: I went back to England, but only for two years, because I had agreed with Joshua Lederberg that I would join his Department of Genetics and start research in the new field of neurobiology. Joshua, in listening to one of my seminars on hemoglobin, I gave at Stanford, said this is a way in which one could begin a study of the brain. You could do the same sort of analysis you did with hemoglobin, just extract the proteins from the brain, separate them by electrophoresis, look for

one whose charge is changed, and come up with mutations of brain proteins. This would give you an entry into studying some of the obvious diseases of the brain, like mental retardation, on the one hand, and perhaps, getting to understand how information is stored in the brain. This seemed a very good idea, and this was the basis on which I was hired. This is what I came back to do. In 1962, while I was still there on sabbatical, Josh wrote a short grant to NIH, in which he proposed a study to look for these proteins; it was readily accepted. He had a technician start to do something with it so, when I came back in 1964, I inherited this grant, which is now in its fortieth year. I've been very lucky to have the support of NIH for that length of time. So we started to isolate brain proteins by electrophoresis and see what we could find. It became clear, fairly soon, that the important proteins in brain were not readily soluble in aqueous solutions. What you could extract, were the so called housekeeping enzymes and proteins, but really interesting proteins, which were involved in electrical transmission down the axons and passing the signal by chemical means from one cell membrane to the other, were membrane bound, and could only be extracted with detergents.

The separation of these proteins was relatively crude and there was no way we were going to see subtle changes. By the time we were discovering you could separate proteins by electrophoresis using an ionic detergent, a scientist called Davis discovered the fact that separation was based on size. This detergent, being highly charged, bound in multiple numbers to the proteins so the separation was on the basis of size, rather than charge. Josh had also suggested that I look at the work of Rita Levi-Montalcini on nerve growth factor (NGF), the name given to the factor that she had discovered that promoted the survival of embryonic sensory and sympathetic neurons. With the help of Stanley Cohen, she showed that the NGF activity was associated with a protein isolated from the mouse submaxillary gland but the nature of this protein was unclear. Silvio Varon, who had worked with Rita joined me at Stanford, in 1964, and together with Junichi Nomura embarked on the purification of the NGF protein. It took almost three years to complete the project, partly because the purification was followed by Levi-Montalcini's sensitive but time consuming biological activity assay and partly because of the need to adapt one of the newer protein screening techniques, acrylamide gel electrophoresis. We finished up isolating an NGF complex, 7S NGF, from the mouse submaxillary gland. The complex contains the basic NGF protein together with a proteolytic enzyme and an inactive enzyme and two zinc ions, which give

the complex significant stability. The NGF protein itself is readily released from the complex and, as Levi-Montalcini originally found, is exquisitely active at very low concentrations. NGF was found in relatively few locations. It is present in the targets of sympathetic and sensory neurons and is retrogradely transported to the neurons sustaining them at critical periods of development. Later, it was found in the hippocampus, and as a consequence, NGF became a factor of great interest to scientists studying memory and learning.

TB: Where did the NGF research lead to next?

ES: We concentrated on the NGF receptors that mediate the effects of NGF and the signaling pathways activated through these interactions. Binding studies identified two NGF receptors on the sensory neurons. We, in particular Monte Radeke and Tom Misko, cloned the first one, a relatively simple single transmembrane receptor, now known as the first member of the TNF family of receptors. It goes by the name p75NTR to indicate its size and its ability to bind all the known neurotrophins. Susan Meakin subsequently showed that the second NGF receptor had tyrosine kinase activity and from its size and location was probably the Trk receptor, a supposition rapidly confirmed by two other groups. A great deal is now known about the way in which the two receptors interact to modify NGF binding.

We identified, with Hans Thoenen's group, the role that NGF and its receptors play in peripheral nerve regeneration and broadened this inquiry to seek other proteins that might be involved in nerve regeneration. We used radio labeling of sciatic nerve proteins and two-dimensional gel electrophoresis to characterize proteins whose rates of synthesis were either markedly reduced or increased after peripheral nerve injury. One protein immediately stood out for its decreased synthesis after nerve injury and its recovery during regeneration. Cloning confirmed that it was a new peripheral myelin protein, whose peptide chain spanned the myelin membrane four times. It was given the name peripheral myelin protein 22 to indicate its location and size. On exploring the structure of pmp22 in mouse models of peripheral myelin instability, harkening back to my days with the genetics of hemoglobin, Ueli Suter identified two separate amino acid substitutions in pmp22 in Trembler and Trembler-J mice. Since these two mice are models for one of the major diseases of the peripheral nervous system, namely peripheral neuropathy (CMT1a), where the myelin sheath disintegrates in late stages of the disease, it strongly suggests that changes in pmp22 cause the disease in humans. This was confirmed in collaboration

with Jim Lupski at Baylor College, but not quite as we anticipated. Jim and his colleagues had just identified the genetic defect in human CMT1a, not as a mutation but as a duplication of a short segment of a particular DNA sequence in one chromosome. I should add that this brilliant discovery was to have a far-reaching impact on human genetics. This sequence contained the normal pmp22 gene indicating that the duplication of this gene was responsible for the human disease, the first gene to be so implicated. Although mutations in human pmp22 have also been found in CMT1a, Lupski and his colleagues have shown that the duplication of the gene is the most common mechanism behind the disease. These findings clearly open up new ways to explore therapies for the de-myelinating diseases, and as anticipated, further genes involved in this class of diseases are being identified.

One of the most extraordinary events of my life was to learn, a few years after the identification of the pmp22 gene, that my own daughter had a peripheral neuropathy. It was diagnosed when she was in her late thirties. Since neither my wife nor I are affected, her disease results from an as yet unknown spontaneous event to her. In my laboratory, further progress came when Jonah Chan, a post-doctoral fellow, made the unexpected but highly important observation that BDNF, the second neurotrophin to be identified, enhanced myelin formation in co-cultures of Schwann cells and sensory neurons. The extension of this approach to see if other neurotrophins are regulators of myelin formation seems likely to produce candidates for therapeutic consideration in the demyelinating diseases. It is extremely satisfying for me to see the two major areas of my decades-long research program come together.

TB: I see.

ES: After many happy and stimulating years in the Departments of Genetics and of Biochemistry, I became the first chair of Neurobiology in the Medical School. Let me give you a little bit of the history behind this. Joshua Lederberg, Donald Kennedy, Avram Goldstein, David Hamburg, and others initiated an inter-departmental Ph.D. program in Neuro-and Biobehavioral Sciences in the early 1960's. Its initial progress was somewhat hampered by concerns at the University level that such a program might be so attractive that it would lower applications to the M.D. Program. As a consequence, advertising the program was limited. Such a concern did not materialize and both programs prospered. With the natural demise of the classical Physiology and Anatomy

Departments at Stanford, the opportunity came to create new Departments. The Department of Neurobiology was formed, in 1975, and we moved into a new building, in 1977.

The initial members were John Nichols and Denis Baylor from Harvard's noted Neurobiology department who had joined the Physiology Department at Stanford two years earlier in anticipation of the expansion of Neurobiology, Jack McMahan also from Harvard Neurobiology, and me. We took over the Neuroscience teaching for medical students and became a focal point for the Ph.D. program, including adding more specialized graduate courses. With the three faculty named above, and other Neuroscience-oriented faculty from the Medical School and University, the course soon became highly rated. The department expanded with the recruitment of Carla Shatz, Eric Knudsen, Richard Aldridge, and Bill Newsome, and reached an enviable level of distinction in both teaching and research. With increased stellar representation of neuroscience in other departments in the Medical School and University, Stanford is well poised for great success in this field.

TB: Are there any other areas of significant interest you want to tell us about?

ES: Yes, my involvement in biotechnology. In the late 1980's, I heard a most stimulating lecture by a young neurologist, Dr. Len Schleifer from Cornell Medical School, on the potential application of the neurotrophins, all four had by then been discovered, as well as others such as CNTF, to diseases of the nervous system. Sometime later, he contacted me to see if I would be interested in joining him to start a biotechnology company focusing on the potential of neurotrophins to maintain neuronal survival. I agreed, as did Dr. Al Gilman, Len's mentor in his M.D., Ph.D. program. We put together an impressive Scientific Advisory Board while Len, realizing he had hidden talents in fundraising, became the CEO, set up laboratories on the old Union Carbide Campus, in Tarrytown, NY. The first scientist hired was George Yancopoulos, recently graduated M.D., Ph.D. from Columbia, and soon after Ron Lindsay, from the MRC in London. The first disease tackled was the motor neuron disease ALS, using CNTF, because it would be easy to deliver it to the appropriate muscles for its uptake and retrograde transport to the motor neuron. Experiments in culture amply confirmed CNTF's role as a survival factor, as did treatment of mouse models of motor neuron disease. However, CNTF failed completely in human trials. What CNTF did was to make the patients lose weight. The explanation came later. The CNTF receptor is homologous to the leptin receptor, whose natural ligand leptin is a regulator of

appetite. Whether CNTF is a drug for obesity remains to be seen. A second attempt in a clinical trial using BDNF also failed, even though markers showed that the patients received a biologically effective dose of BDNF. At the present, it is not possible to try the combination of CNTF and BDNF that also prevents motor neuron disease in mouse models because of the FDA requirement that the components have to be effective and safe when administered singly, before they can be used in combination. These examples show how difficult it is to develop a new drug.

TB: How would you summarize your career?

ES: It has stretched over 50 years of research and teaching, mainly at two institutions, University College London and Stanford. At both institutions, I have been privileged to work with a series of bright undergraduate and graduate students, postdoctoral fellows, and sabbatical visitors. I have learned much from them and gained great satisfaction from their subsequent successes. Each institution has provided a wealth of distinguished colleagues and I cherish the friendships that have formed over the years. Thanks to the flexibility of research funding, particularly from NIH, I have been able to follow projects with unforeseen but highly profitable directions. My elder granddaughter, when asked in high school what she would like to be replied, “a neurobiologist.” When asked to explain she answered: “My Grandfather is a neurobiologist and he enjoys his work very much.” That just about sums it up.

TB: Where would you like to see things move in your area of research?

ES: Very much along the lines on which science has developed in this country. The NIH support of research, both intramurally and extramurally, is excellent and the recent doubling of the appropriations by Congress speaks volumes to the high regard NIH is held in Congress. It is indeed one of their major successes.

TB: I think this would be the right note to conclude this interview. Thank you very much for sharing all this information with us.

ES: It was my pleasure.

TB: Thank you.

59. GEORGE M. SIMPSON

TB: This will be an interview with George Simpson⁶¹ for the Archives of the American College of Neuropsychopharmacology. We are at Tulane University, in New Orleans. It is May 9, 2001. I am Thomas Ban. We should start at the beginning; where and when were you born and could you say something about your education?

GS: I was born in Pennsylvania, which surprises a lot of people. My family came to America after World War I and my father worked as an electrician in the coal mines. My brother and I were born in the U.S. When I was two and a half, my father died. Soon after, I went back to Scotland and grew up in a small town in Lanarkshire. I went to school there, then, junior high five miles away, and finally I went to Glasgow University and studied biochemistry. I volunteered to enlist in the air force but they deferred me because the war was coming to an end. This was 1944, so I stayed and graduated. They didn't have an organized course in biochemistry, so what I did was physiology and chemistry. I was a terrible student, in the sense I had a lot of fun and a lengthy adolescence. After graduation, I had to do work of national importance. They sent me to work with Distillers in Liverpool, who made Scotch whisky and antibiotics; I was unlucky enough to get the antibiotics. I worked there for two years; it was interesting and I enjoyed it. It paid well so I applied to college and stayed another two years, working in the summer for ten weeks with Distillers, which helped financially.

TB: When did this happen?

GS: From 1948 to 1950. I started medical school in 1950. I was a good student, I liked medicine and I studied harder. I finished in 1955 and did a compulsory year internship, six months in medicine, which included neurology, and six months in surgery. Then I applied for a fellowship in France. I was short listed and when I was interviewed and asked why I wanted to go to France, I waffled and told them because I was going to do pathology. The interviewer looked at me and said, "Which country in the world do you think produces the most pathologists per head of

⁶¹ George M. Simpson was born in Pennsylvania in 1926 to Scottish parents and returned to Glasgow, United Kingdom, as a young lad following the death of his father. He graduated as a physician in 1955 from Glasgow University. He trained in psychiatry at McGill University and Rockland State Psychiatric Hospital. He transitioned to becoming one of the early ECDEU investigators in which capacity he was able to take a look in his patients at almost every antipsychotic drug before it came on the market. Additional academic positions have included stays at UCLA and Medical College of Pennsylvania. He was interviewed in New Orleans, Louisiana on May 9, 2001

population?” When I said, Scotland, he replied, “So why would you want to come to France?” After that I was reading the *Lancet* and saw an ad from McGill for applicants in their psychiatry training program. I wrote a letter in long hand and received a cable from Ewen Cameron accepting me. He’d never seen or met me before!

TB: So, you moved from pathology to psychiatry?

GS: Pathology was just a reason to spend a year in France. I had been interested in pediatrics and psychiatry and eventually decided I’d rather do psychiatry. The department at Liverpool wasn’t that good. Frank Fish was the first Chair, but he came later. They had only a Reader at the time, so I thought of going to London, but instead chose Montreal.

TB: Could you tell us something about the training program at McGill?

GA: I thought at the time it was good. In retrospect, I think it was superb; it was probably the most eclectic program that has ever existed.

TB: Tell us something about the faculty in the department of psychiatry.

GA: Eleven to thirteen people there at the time became Chairs of Psychiatry. Charlie Shagass was doing sedation threshold work predicting the outcome in depression. Bob Cleghorn, who succeeded Cameron, and Bruce Sloan, who became chair in L.A., were supervisors of mine, as was Jim Tyhurst, Robin Hunter, and Tom Boag, two of them became Chairs. Clifford Scott, who was president of the international psychoanalytic movement, was in the department. He was a nice man but I discovered it was difficult to understand what he was talking about. Azima was there and Prada, who was a pupil of Cajal, and Ted Sourkes, a biochemist. It was probably the only department in North America that had a steroid chemist and a catecholamine chemist within a department of psychiatry. Malmo was doing his work on galvanic skin response to measure anxiety. So it was interesting but a bit confusing for a young doctor; it made you read because it was very competitive. That was the first time I did that in my life in medicine; I felt everybody knew more than I did. During the first three weeks, I read from cover to cover Frieda Fromm-Reichmann’s *Principles of Intensive Psychotherapy*, Anna Freud’s *The Ego and Mechanisms of Defense* and Bleuler’s text on *Schizophrenia*. I studied the lingo so I could talk rubbish with the rest of them. And Cameron was a marvelous administrator, but a terrible researcher.

TB: Did you have any contact with Cameron?

GS: I was on Cameron's service and he had a number of Scottish private patients he handed over to me. We used IV methamphetamine as a diagnostic test and people were giving LSD as the royal road to the unconscious. We were trying everything, even though, looking back, some of it was naïve. John Davis and Dave Janowsky wrote a paper on using methylphenidate, a dopamine agonist, as a diagnostic test in schizophrenia without realizing it was used as a routine at McGill twenty years before. We gave a lot of electroconvulsive therapy and we still used insulin in the treatment of schizophrenia. I found, afterwards, that I missed it. It was like a big family.

TB: Several people in the department were involved in psychopharmacology research at the time you were there.

GS: Yes, Sarwer-Foner and Bruce Sloan were doing some work in psychopharmacology, and of course, Heinz Lehmann was doing a lot.

TB: So, Bruce Sloan was involved with psychopharmacology in those years?

GS: Yes, and I don't remember who, but someone was working with perphenazine. There was a room for sleep therapy, a treatment used in Russia, extensively in those years, and a day hospital, where ECT was used with anesthesia and muscle relaxants. When I went to New York, they were giving ECT without any muscle relaxants or anesthetic; I couldn't believe it! I was even lectured on how silly it was to use them.

TB: Could you say something about Cameron himself?

GS: Cameron was a very interesting man; he had two great young analysts, Robin Hunter and Tom Boag, and he put one in charge of ECT and the other in charge of insulin. It made them into all-round psychiatrists, and they were both terrific people. I told Heinz Lehmann I was disappointed I didn't see more of him. He was really an all-rounder. TB: So, you were in contact with Heinz Lehmann?

GS: Right. After what was a stimulating year, I applied for every program in the States that took foreign medical graduates, was approved for three years that paid trainees \$300.00 a month. Those were my criteria; I sent out about three dozen letters and a few days later, Cleghorn told me he had a call from Nate Kline, in New York. That was the only place I interviewed, because Nate invited me to Rockland State Hospital, where he had a research group that was stimulating.

TB: When did you move from Montreal to New York?

GS: In 1957, when they were involved with reserpine and monoamine oxidase inhibitors. Nate had a big private practice, where he put patients on new drugs to evaluate them. They were mostly uncontrolled studies, a complete waste of time, with small sample sizes, but I participated in one of them. In the only clinical paper that Brodie has his name on, he wrote that imipramine was demethylated and had alluded to animal models, in which desmethylated imipramine acted as an antidepressant. Since it was a metabolite of imipramine, he suggested it might act faster than the parent substance.

TB: This was in 1962, wasn't it?

GS: That would be about right. I was co-author of the paper.

TB: Did you find that desipramine did have a faster onset of action than imipramine?

GS: You couldn't tell, because in all depression studies, you get this big improvement in the first week. I've forgotten the sample size; it was something like 22 patients, so there would be no way of knowing without having a control to arrive at that conclusion.

TB: What else were you involved in at the beginning?

GS: I ran a research ward; we were interested in the Gjessing Syndrome, so we had a couple of patients diagnosed as periodic catatonia.

TB: How did you diagnose patients with periodic catatonia?

GS: It was a clinical diagnosis but not a lot came out of that study.

TB: What else were you involved with?

GB: I wrote a grant for measuring endocrine status to predict outcome of drug treatment. Jonathan Cole said he thought it was a good idea, but we should expand it. I was too junior to be the project director, so Nate became the principal investigator. Eventually, we got a paper out of it, but I didn't put my name on it because I felt there was nothing there. Then I collaborated with Ted Cranswick on a project about thyroid function that turned out to be a false lead because institutionalized patients were fed iodized salt. I also collaborated with John Blair, studying the semen of patients.

TB: Could you say something about the people at Rockland? Were Saunders and Barsa still there?

GS: Saunders was there and Barsa, as well. Barsa and Saunders were originally working with Nate on reserpine, until Saunders came along with the monoamine oxidase inhibitors. He had some notion that monoamine oxidase activity might be related to the effectiveness of those drugs. Saunders was not a psychiatrist, so they got some young doctors in the admission wards to treat

patients and report back. I thought that was pretty awful. So I decided to get involved in treatment and did a study with Saunders on a butyrophenone, a Wyeth drug. After that, I started working on my own, because it seemed to me that Saunders was having trouble with Nate. It was then that I applied for an ECDU grant.

TB: You mentioned briefly that there were some problems between Saunders and Nate. Could you elaborate on that?

GS: It was about the introduction of MAOIs. They gave a paper on iproniazid on which Nate was one of the authors. Nate ran with it and publicized it, but after he got the Lasker Award, he wrote an article, I think it was in the *American Journal of Psychiatry*, claiming most of the credit and Saunders sued him. I think Nate was the right man in the right place to publicize it, but he could have given more credit to the other authors of the paper. That suit went on for ages, and obviously, was disruptive. Saunders did eventually take residency training, but then moved out of the field altogether. Eventually Saunders won the case, but the judge, after all those years, gave them a third of the award's ten thousand dollars. They must have had a fair amount of lawyer's bills.

TB: What about Barsa?

GS: Barsa worked in a large building where, it'd be safe to say, there were at least 500 patients. He and another doctor took care of them all. It's very hard to do research in a situation when one is looking after all the physical and psychiatric problems of so many patients. He did part of the reserpine study in that building, relying on casual observations. There is a story that they nearly missed the efficacy of reserpine. It was a hospital glazier who stated that at the time the study was done, there were less cracked widows on the ward than ever before.

TB: Still, Nate Kline played a role in the introduction of both reserpine and iproniazid. Would you give credit to him?

GS: Yes, Nate deserved credit for the fact that his practice was strictly pharmacological. His practice was interesting; I used to cover for him when he went away, because he used to take six weeks of vacation, mostly to attend the Salzburg music festival. When I covered for him, it was interesting to get many referrals from other psychiatrists and psychologists for his opinion. There were clinical trials done in the office, and we attempted to use controls, but that was difficult because Nate liked to use a touch of this or that, from whatever was available at the time. In one of the studies, it could have been desipramine, Paddy Watts, who was working with us at that time,

did the diagnosis, I did the rating, and Nate did the treating; but when I broke the code, Nate had added other drugs to half of the patients. It was in that office they did the endorphin study that got Nate into trouble.

TB: Wasn't the endorphin research done much later? GS:

Much later, yes.

TB: Didn't you do some research with histamine in schizophrenia in those years?

GS: That was done on Nate's suggestion. Clearly, there was a difference in histamine sensitivity in schizophrenia compared to a matched group of organic patients.

TB: Didn't you do some research on the effect of drugs on sexual behavior?

GS: That was done in the 1970's. I treated one of my colleagues, who got depressed, with Nardil (phenelzine) and he awkwardly told me that he had been a control in clinical studies and measured his sperm count twice a week for the last couple of years. When he looked at the figures, he saw that, after Nardil, volume, count, and motility went up. When his assistant got depressed and I treated him with Nardil, he was also a control and the same thing happened. Then, hard to believe, there was a third person in the lab who got depressed. I felt I should write it up and publish it as a letter. The subjects were three researchers, but Nate wanted his name on this paper. Sometime later, there was a snippet in Time Magazine about somebody in Vermont who bought a magnificent and expensive Argentine bull, which was producing no sperm, and Nate was giving the bull Nardil. Later on, I found out that the three researchers had been drinking heavily but had to get off alcohol before I gave them Nardil; their sperm count increased after they stopped drinking, so it probably had nothing to do with Nardil. That was an interesting little diversion!

TB: Could you tell us how you got involved with ECDEU?

GS: That was after I had done my first drug study with Jack Saunders and met with Jonathan Cole. When I received my NIMH grant, I also got another 40-bed ward. And I became involved with an interesting group of people; Don Gallant, Art Sugerma, Sid Merlis, Hy Denber, and many others. The first meeting I attended was in Palo Alto with Leo Hollister. Probably at that time, I knew every psychopharmacologist in the country. There was camaraderie, and a fair amount of fun.

TB: Did you participate in the ECDEU program from the beginning?

GS: These other people were involved before me, but it was early on. We worked sort of independently and it was left up to you, what you did and how you did it. You could have said it

was a government intervention to make it easier for the pharmaceutical houses to develop drugs. It was one way of selecting a group of people who could study drugs better. Nearly all of these places were not in academia. Don Gallant and Leo Hollister had inpatient units. So did Sid Merlis and Hy Denber, but in state hospitals, as I was, or in VA hospitals. So it was a marvelous productive idea that set the ball rolling. I feel it wouldn't be a bad idea to bring it back because there is a concern about the objectivity of some of the assessments today. Today, they are talking about how pharmaceutical houses design the studies, their staffs manage the data, and clearly nobody is totally free of bias. By being totally independent and in control of the situation, the ECDEU investigators could look at whatever drugs they were interested in. In the early 1960's, I looked at Tegretol (carbamazepine) in schizophrenia, before the drug even had a name. It produced the most unquoted paper I ever wrote, but it was the first time Tegretol was given to psychiatric patients.

TB: When was that?

GS: I presented it at the CINP Congress in Birmingham, in England, in 1964. I sent the paper to the *British Journal of Psychiatry* and they said, this drug will never be used, certainly not in Britain. I never sent it anywhere else, so it was only published in the proceedings of the meeting. Actually, it showed that you could convert people from multiple antiepileptic drugs to just one. Nearly all the patients managed to be maintained on Tegretol, alone, rather than the two or three anticonvulsants beforehand. We also did dosing studies and looked at extrapyramidal symptoms (EPS). It was during the 1960's that we developed a rating scale for EPS, and I first published about that, in 1964. All the antipsychotic drugs produced Parkinsonism and until then, there wasn't any scale for assessing it. We thought if you could quantify it, it would be easier to look at the potency of drugs relative to that side effect rather than psychopathology. So we developed the scale when Scott Angus was working with me. We also published a whole series of papers, in 1970, on the scale. I never thought people would use it like they ended up doing. It was designed for use in inpatients. It was not to detect questionable EPS, but to look for definitive EPS.

TB: That scale has certainly been used widely.

GS: We modified it a little, because not every outpatient clinic has a table or couch. With the new drugs, most of these scales are probably not too helpful because there is very little EPS. It would be interesting to go back and look at handwriting that detects sub-clinical EPS, with the new drugs,

like olanzapine. We did a lot of work on handwriting in the 1960's. That showed that low dosages worked as well as high dosages.

TB: Could you tell us more about the handwriting test?

GS: Haase suggested that there was a very good correlation between minimal changes in handwriting and the therapeutic dose. He also suggested these minimal changes were subclinical; in other words, you could see changes in the way somebody wrote long before you could detect changes in a patient's gross or neurological status. Haase read them by inspection, saying this is normal or abnormal. Clinicians did that very well with the EEG until it was quantified with the introduction of computers. Since no one did that with the handwriting, we started to develop various ways of quantifying change. Then Phillip May developed an automated handwriting test and was going to send it to me, but he unfortunately died before he got around to it. I don't know what happened to the handwriting test, it sort of dropped out of use. One problem was you couldn't get every patient to write for you. But it was useful. By the time haloperidol reached these shores, Haase was saying that the therapeutic dose of Haldol was less than 5 milligrams. Current dopamine receptor occupancy PET studies suggest that 5 milligrams gives about an 80 percent blockade. So, I think we overdosed widely and, to an extent, harmfully, despite the handwriting data. If it had been easier to quantify, we might have been able to convince people to use it.

TB: Could you tell us about the drugs you worked with in those years?

GS: We looked at a Wyeth drug that never got a name and we looked at trifluoperidol, both of which lowered cholesterol levels dramatically. Then, we looked at haloperidol and cholesterol levels; there was no effect. The FDA had asked for information on that. We validated our rating scale in the haloperidol study because we saw that 30 mg. caused a lot of EPS, compared to 6 mg. We studied thiothixene and loxapine before they came on the market. We did a study with a Pfizer drug that produced liver function abnormality and never made it, so not everything was marketed that we looked at. Finally, I think the pharmaceutical companies realized all of these drugs, from an efficacy point of view, were the same and that there were different side effects. So they needed a new kind of drug and the clinical response to clozapine stimulated interest.

TB: When did you work with clozapine?

GS: About 1974, and we published a paper on its effect on tardive dyskinesia, in 1978. It was interesting because the nurses on the ward knew immediately it was different. They saw

improvement, a lot of sedation, a bit of hypotension, no EPS, improvement in TD, withdrawal effects, and seizures. Seizures might be related to the high plasma level that these patients had, but later, I thought it might be related to the sudden increase in dose rather than in plasma level. One of the incidents was a suicide attempt, and the other one, an accidental double dose. We looked at metiapine, and that's the only drug I felt absolutely convinced did something to a patient whom I have known for years that nothing had helped, including loxapine and clozapine, to which it's related.

TB: What did it do?

GS: This was a patient who was a paranoid schizophrenic, who felt the Queen of England had visited him at Rockland and with metiapine all the delusions disappeared.

TB: What happened to the drug?

GS: They decided not to market it. I think it was the same Swiss company that had clozapine and loxapine. I suspect if there had been more of these kinds of cases, they would have pursued it.

TB: Could I ask you to say something about documentation of changes, in general. We know that in the early 1960s, it was very poor. When did that change?

GS: I think the ECDU was instrumental in changing it.

TB: Could you elaborate on that?

GS: Eventually ECDU, as a group, decided we'd use the BPRS and the NOSIE in all studies. What that meant was you could compare studies. If you wanted to use other scales, that was fine, but these were the scales that went with the database. Out of that came ECDEU's documentation system, in which Bill Guy was involved. He developed a series of forms that made it possible to use standardized documentation of a clinical trial with a number of rating scale prepared for optical scanning.

TB: Wasn't Rockland State computerized rather early?

GS: They brought in a statistician, a young man, Gene Laska who worked with IBM, who set up a computer system and eventually everything was computerized. It was too far ahead of its time, the doctors hated it, and the administrators loved it. At that time at Rockland, drugs could be rationed if there was a budget cut, but I don't think it ever happened. So every building had their private pharmacy, in case they ran out of money. When the drug prescribing was computerized,

you couldn't order more than you required and the large inventory of drugs present at each buildings could no longer be increased for the hypothetical rainy day. Later, everything was on optical scan sheets and the computer produced a differential diagnosis, an anamnesis, and translated the numerical ratings into English words. In 1974 or 1975, I had an inpatient and outpatient unit where everything was computerized. We had a full drug history with all the information that could take weeks to find out, for example, the reason for prescribing the drug, the reason for increasing of dose, the reason for addition of another drug as Cogentin (benztropine mesylate).

TB: Didn't you have a specially developed mental status?

GS: Right. The first mental status was created by Paddy Harper, Gene Laska, and me. Paddy was from Ireland and came to work with me. He did a lot of the work on developing the mental status and embedded a Hamilton Rating Scale and a Wing rating scale for schizophrenia in it. You completed the optical scan form, entered it into the computer, and you received a printed sheet in reasonable English with rating scores to the above scales. At the World Congress of Psychiatry in Madrid, you could fill in the NOSIE in English and get the printout in six languages. I have a Russian publication on that. That was a lot of fun, it was helpful and I wish it would have lasted. Bob Spitzer came and worked on a second mental status examination with a narrative output and a marvelous storage system, but psychiatrists felt it was imposed from above, and didn't like it. We set up guidelines for prescribing, with the computer indicating that (1) this is okay; (2) do you really want to do that? (3) this is questionable; and (4) not permitted. That irritated a lot of people. I thought it would be good if people would know which drugs were best. Many psychiatrists prescribed haloperidol, which cost ten times more than fluphenazine, and nobody could differentiate between the effects of the two drugs. Gene Laska was very helpful. I'll always regret that, when he wanted me to have a cathode ray tube on my desk in the early 1970's, I said, Gene, "Why should I have anything to do with computers, when I can pick up a phone and call you?" With hindsight, I should have done it; I would have been much better at working with computers than I am. It also helped us in our research. I can remember one time I did the last assessment in a project at 11:00 AM, and when I came back after lunch all the data were on my desk analyzed. Gene was involved in the first study which showed that you got withdrawal effects after stopping drugs, but it was from stopping the anticholinergics and not the neuroleptics; the anticholinergics

were the culprit. So, we did a controlled study. First, we treated patients to produce a quantified amount of EPS using trifluoperazine; it took from 20 to 500 mg for different patients. Then, they were kept at this dose for an additional four weeks, at which time, they were abruptly withdrawn. We didn't see anything! After the patients were drug free for four weeks, they were treated in the same fashion to see if the side effect were the same on both occasions. After they reached the full dose and they were on this for a month, we added benztropine mesylate for a month, and when we withdrew both drugs, we got all sorts of problems. We also found that the anticholinergic drug sensitized patients for EPS. We followed that up in several studies. Then we did a three months dose response study with butaperazine after each patient were taken off drugs for a month, and when they were put back on butaperazine, even on lower dosages, they had far more EPS than they had the first time. We didn't measure blood levels. We did a lot of studies like that, filling gaps in our knowledge, which was fun.

TB: When did you start to do blood level determinations?

GS: Somewhere in the late 1960's. There was a phenothiazine meeting and Irene Forrest gave an account of measuring phenothiazine metabolites in the urine. But most antipsychotics had many metabolites; I remember someone saying that chlorpromazine could have as many as 160 metabolites. So it was a nightmare. Then, we looked at butaperazine because we felt it might be easier to measure blood levels and we did some interesting studies. We also did blood level studies with loxapine and with lithium. But no one could ever show that measuring blood levels of antipsychotics was very helpful. Clozapine might be the only exception. Still, it had to be pursued because it was possible it could explain why some people respond, whereas others don't. I don't think anybody measures blood levels any longer.

TB: Didn't you measure lithium blood levels after a loading dose to predict response to treatment?

GS: Right. We had an M.D. from Sweden who was good at physics and mathematics and was modeling complicated kinetics of lithium after multiple blood draws over a 24-hours period. They were then treated therapeutically with lithium. The laboratory technician phoned me and stated that this patient had the highest 24-hours blood level he had ever seen and questioned it. We then took another blood level even before he was at steady state which showed a very high lithium level. This led to us giving a loading dose of 600 mg with blood taking 24-hours later. Inspecting a table created from the raw data gave you an approximate dose required to approach a therapeutic

range. It was useful particularly for outliers. The trouble was, you needed to measure lithium levels to the second decimal point and a lot of labs don't even give you the second decimal point, some of the machines don't read it. If you have a lab that does blood levels with the necessary precision, it speeds up getting to steady state. We used a similar technique with loading doses to predict the amount needed to get into the therapeutic range with desipramine and nortriptyline. That would have been useful, but again, it never took off. We used it at Rockland and other people used it too. Tom Cooper, in the lab at Rockland, automated the techniques and developed methods for measuring blood levels of antipsychotics, antidepressants, and lithium. He did lithium levels using saliva and micro amounts of blood from finger pricks. So people like Gene Laska and Tom Cooper made life easier for me. We used lithium very early on in half gram capsules, which we made up ourselves. I used to give everybody 1800 mg a day until we got a blood level and then we adjusted the dose. We didn't really know what the therapeutic level was, and we were shooting for about 2 meq/l. Surprisingly we did not get a lot of toxicity. We were probably just lucky.

TB: Let's get back to chronology. Could you say something about your early studies with ECDEU?

GS: Power analysis didn't exist, so we did studies that were really under powered and even though we did some collaborative studies, the sample sizes still were not big compared to today's samples. On the other hand, in current studies, investigators and the sites are very heterogeneous, so you need to have large samples.

TB: Do you have any preference for single center or multi-center studies?

GS: We need them both. The kind of studies that were being done in those days would be hard to do today.

TB: For example?

GS: A dose escalation study. The doses, calculated from the animal data are helpful, but can be misleading. We found out a lot about drugs that way; but people would turn up their nose at that kind of study today saying the dosing information was contaminated by the fact you kept increasing it. It was not difficult for an ECDEU unit to do a study of 10 patients, and from that tell a lot about a new drug. I remember a drug that I studied with 12 patients, and it was definitely active, but when we got liver function tests, they were higher than we would have liked and one patient had a seizure. We did a multi-center study at four sites in which Don Gallant and Art

Sugerman were involved. In the larger sample, there were three or four abnormal liver function tests and two seizures. We exposed less than 50 people to the drug and were able to say it was active but with too many side effects.

TB: Did you use the handwriting test in some of those studies?

GS: We did and, for instance, with clozapine we saw that handwriting increased in size, something we'd never seen before. With all other active drugs, we got diminished handwriting area. Clozapine was an incredible advance in therapeutics as well as a huge incentive for research.

TB: Did your findings with the handwriting test correspond with the recommended dose?

GS: Yes, but what you saw, was that if you allowed doctor's choice of dose, they might give up to 400 percent more than handwriting dictated. I always felt that, from a clinical point of view, it made sense to keep on increasing the dose until you got side effects, as long as you realized that by the very nature of that process, you would give more than you needed, and then you should back off. But people often didn't do this and so we had a generation of high dose treatments that was not helpful.

TB: Didn't you have a study designed for testing the correspondence between the dose based on handwriting test and clinical judgment?

GS: Eventually, we did a double blind controlled study, where I had one M.D. who trained with Haase who knew nothing about the patients but read their handwriting one day a week. In that study, for half of the patients the dose was based on handwriting changes and in the other, on the judgment of the psychiatrist. There was no difference in outcome but there was in dosage. Doctor's choice was more than double compared to that of the handwriting group. The psychiatrist made the recommendation for the increase of dosage but if the patient had reached the handwriting threshold, I did not write the order. In general, psychiatrists tended to use high dosage in spite of the fact that there was never any evidence that higher dosages improve outcome.

TB: Weren't you involved in testing drugs with an effect on methylation in schizophrenia?

GS: There was a drug for psoriasis with an effect on methylation; and I tried to recruit several patients who had schizophrenia and psoriasis and sent them to the dermatologist in the hospital. But the dermatologist got so enthused about the project that instead of giving the drug orally, the way he would normally, he decided he would give it in intramuscular form. Because we had to

order it, the hospital administration got worried about the study and it never happened. Various companies had drugs that inhibited methylation, but we didn't have much to do with that.

TB: Didn't you try antidepressants in schizophrenia?

GS: There was always a fear that if we gave antidepressants to schizophrenics it would over activate them. We had a group of patients with chronic schizophrenia, who had been off drugs for a month, and we gave them 300 mg of imipramine for a month; but apart from dry mouth, we didn't see anything. I think Don Gallant gave even higher dosages in a study. We tried all of those things with the hope that one might have an effect. When I was an intern, in 1955 and 1956, I used chlorpromazine as a hypnotic, an antihistaminic, an antiemetic, and an antipyretic, as well as for hypotension and for neurosis. It has some effect in all those conditions, but for all of them, there are better drugs available today.

TB: You said that you did some early studies with clozapine. Were you involved in studying any of the other atypical antipsychotics?

GS: Yes. Clozapine is a unique drug and it is still the best, but it is a difficult drug to use and not only because of the white cell monitoring. It's a difficult drug to dose in that you can get hypotension and many other side effects. So we became interested in other atypicals. Risperidone was the first drug in that group; it was designed to affect the serotonin system as well as dopamine system. In fact, it was the first designer drug in psychiatry. We studied it and found it a useful drug with good patient acceptability. That feature certainly helped atypical antipsychotics to advance. If you look at all the studies, it's much easier to separate haloperidol from quetiapine and other atypicals by EPS than by psychopathology. The fact they produce less EPS is a distinct advantage, and compliance issues should be better for the atypicals. So, after clozapine, we worked with risperidone. Then, we did a little bit with quetiapine, and quite a lot with ziprasidone. We did work with olanzapine both in animals and in adolescents.

TB: Thioridazine, one of the first phenothiazine neuroleptics, produces less EPS than haloperidol. If my recollection is correct, you did some research with thioridazine, didn't you?

GS: In the 1970's, there was an editorial in the *BMJ*, which said someone had been to a geriatric meeting and the only thing people from the U.K. and U.S. agreed on was that thioridazine was the drug of choice for the elderly, which seemed to me a bit odd and wrong. So, we studied a group of elderly patients with schizophrenia and an average age of 67, range from 60 to 81, who were

off drugs for a month. Then under double-blind conditions, they received either fluphenazine or thioridazine for eight weeks, then off medication for a month, and then crossed them over to the other medication for another eight weeks. We saw more EPS with fluphenazine, and more hypotension and weight gain with thioridazine. But the main finding was prolonged QT interval in 9 out of 30 patients on thioridazine, and none on fluphenazine. Recently thioridazine got a black box warning from the FDA because of its prolonged QT. Our study was published in 1978. I stopped using thioridazine of that time. So, that study with thioridazine, I thought, was useful and clearly differentiated side effects between the drugs. The fact there was more EPS with fluphenazine validated the NIMH 1964 study that compared fluphenazine and thioridazine with chlorpromazine, in which they saw more sedation with chlorpromazine and thioridazine, but more EPS with fluphenazine. Fluphenazine and thioridazine were new drugs when that study was carried out. There was no difference in their effect on psychopathology, which is true for all antipsychotics until clozapine. That is a difference in side effects but not an efficacy.

TB: Wouldn't that apply also to the atypicals in general?

GS: I think that's true. The atypicals are, within limits, equal from an efficacy point of view. We have a poster at this meeting on our findings in a comparative study of ziprasidone and olanzapine. There was no difference in their effect on psychopathology but there was more weight gain with olanzapine. There was some indication of more EPS with ziprasidone. If you took somebody off haloperidol and gave them olanzapine or risperidone, you would be able to separate them on the basis of the EPS very quickly but it would be hard to show differences in efficacy. I think the CATIE study is useful, even though it's very complicated, because you need an independent group of people to do such studies. At the annual meeting of the ACNP, a year ago, I commented that you don't have to read the posters of these comparative studies of atypical antipsychotics. The sponsorship of the trial seems to dictate what the results are going to be. I don't think people cheat, but they are unlikely to design a study that could go against what they'd like to see.

TB: Did Sy Fisher write something about that?

GS: Yes, he did.

TB: Didn't you study the relationship between negative symptoms and EPS?

GS: The increase of negative symptoms paralleled the increase of EPS. We showed that there is a correlation between what's rated as a negative symptom and EPS. So, if you don't get any EPS,

you're bound to be better on negative symptoms. My other thought is that akathisia could exacerbate positive symptoms and relate to poor outcome. Actually that was shown in our study with fluphenazine. Ted Van Putten wrote a lot about that. Akathisia is very undesirable. If you have less akathisia and less rigidity, the outcome is better. And don't forget, you can not only get bradykinesia from these drugs, but also bradyphrenia, slowed thinking; the key question is, are there any differences between these drug-induced symptoms and primary negative symptoms? I doubt it.

TB: Is there is really any difference in efficacy between the older antipsychotics and the newer atypicals?

GS: I really don't know. John Davis just published the findings of his meta-analysis in the British Medical Journal. He gave me a copy yesterday, I haven't read it yet, but he came to a different conclusion. But whatever his findings are, clearly they represent an advance, but how large of an advance remains unclear. The real problem is that people are struggling with their price. I have a concern because, in the United States, we're soon going to feel that to use typical antipsychotics is malpractice, and that bothers me. I just got an e-mail from another university sending me a study that would compare long acting haloperidol and an atypical in the maintenance treatment of schizophrenia; the question was, is this ethical? To me, that's strange, because you have one of the best treatments for maintenance and another that's never been studied for that. My prediction would be that there would be more side effects in the haloperidol decanoate group, but more hospitalizations or relapses on the atypical. So, I think we are throwing the older typicals out the window very quickly. I recently interviewed a patient who was on a study and he insisted that the best treatment he ever had was haloperidol. There's going to be a handful of people who might very well prefer that.

TB: Do you think that all schizophrenic patients benefit more or less equally from treatment with antipsychotics?

GS: No. If you take John Davis' meta-analysis, you have 30 percent of people who are treatment resistant who improve with clozapine; but if you look at risperidone, it would probably be about 15 percent. If you assume that 60 percent of people don't do terribly well on typicals, and it might even be a bit higher over a long time, you're still seeing a large number of patients who are not going to do all that well on atypicals; there are no miracles. I've always had the suspicion that

many people who did so well on clozapine were probably affective disorders. There's always been the notion that a percentage of people with schizophrenia do not respond. It's fascinating because, 20 or 30 years ago, if you gave a lecture and talked about taking people off neuroleptics, it would have been enthusiastically received. Now by many, it's considered unethical. Clearly, if you have patients in a defect state or have a chronic illness, whether you give them an antipsychotic drug or not, doesn't make much difference. In fact, if you're giving them a drug that makes them over sedated, feel fuzzy, or could give them some other side effects, they would feel better without it.

TB: Do you remember that in the early 1960s, Frank Fish classified schizophrenic patients on the basis of Leonhard's criteria and found different responsiveness in the different groups?

GS: Frank Fish came to Liverpool after I left. Clearly, Leonhard's classification has had more impact with German and Continental psychiatrists. It's certainly not the classification we use. Frank Fish was remarkable. He was a London Jew, who was a prisoner of war in Germany, learned German, and became the English expert on German psychiatry. His book on *Schizophrenia* is very good. This classification would suggest probably 13 different sub-groups of chronic schizophrenia. I don't know that anyone has looked at it in substantial numbers in terms of treatment outcome.

TB: Do you have any notion how we should proceed in this area of research to break the impasse?

GS: My notion would be that at least in some schizophrenic patients there are identifiable abnormalities at a very early age and that might be one group. Probably one of the best things for schizophrenia would be good obstetric care. In the 1930s, about a third of people in Scotland were improperly nourished. Because of rickets, there were many women whose pelvis was too small to deliver children, and the lower Cesarean sections hadn't been introduced and there were many prolonged labors. One thing the war did in Britain was that, for the first time, the whole country was well nourished. This would result in fewer difficult labors in the future and the lower C section was introduced, I believe, in the 50's. Then one would have to investigate what early interventions might do to outcome. In addition, pharmacologists are looking at the NMDA receptors and other areas to find new drugs for schizophrenia. Dopamine blockade was a significant finding but it turned out to be slightly simplistic.

TB: So, you think we should be moving towards early detection and intervention?

GS: Yes.

TB: When you entered the field, chlorpromazine and reserpine were already used in schizophrenia. Wasn't a butyrophenone the first drug you studied in schizophrenics?

GS: I'm not sure, but I studied thiothixene, molindone, loxapine, clozapine, and a number of other drugs that never made it to clinical use.

TB: What was the last drug you studied?

GS: Ziprasidone; and we've carried out several studies.

TB: Could you tell us about your findings?

GS: It differs in one respect from many of the other drugs; it doesn't have as much of an effect on the histamine (H₁) system and you don't get weight gain. And it is as good an antipsychotic as the others. This has to be seen against the background that more and more people are reporting weight gain and Type 2 diabetes with drugs like clozapine, olanzapine, and quetiapine. In our six-week study on ziprasidone, we had one woman who lost 18 pounds in six weeks. She had gained it on previous drugs. It's not as if it's a weight reduction drug, but that aspect was helpful. For the group as a whole, there was a five and half pound mean weight difference at the end of six weeks and that is a lot. So, if you have somebody who is very overweight, you might give them ziprasidone. We looked at the drug in inpatients and outpatients and it was very acceptable to patients without a lot of troublesome side effects. The QTc prolongation present has been much exaggerated.

TB: What was the sample size of the study?

GS: This was a multicenter study, so there were a few hundred patients. In our own outpatient study, we had 39 patients and at the end of six weeks, there was a significant reduction in cholesterol and triglycerides. The same was seen in the multicenter study that had about 260 patients, again there was a significant reduction in cholesterol and triglycerides compared to olanzapine.

TB: You were also involved in clinical investigations with antidepressants. You mentioned that in the early 1960s, you studied desipramine.

GS: That was in the outpatient private practice of Nate Kline. There was one year we saw 400 new patients, the vast majority were seen by Nate himself. That is a very large number, when you think of today and the difficulty of recruiting patients for depression studies. But there was nowhere else for them to go; most of them were or had seen a therapist and some had lengthy

analysis. Albert Ellis and another psychotherapist referred patients, and patients came looking for treatment; so it was much easier to do research. The trouble was we could do only a few controlled studies. You could argue that we did not use placebo, but most of those patients had never used drugs before, and you really did see people who made dramatic improvement and would tell us that they felt better than they had in years. They improved dramatically. I don't think one sees anyone like that today because family doctors, gynecologists, and internist are treating a lot of them.

TB: Weren't you involved in research with MAOIs?

GS: Right, I still have an interest in them. There is a range of studies that show that people who failed to respond to tricyclics would respond to MAOIs.

TB: You worked with phenelzine and tranlycypromine, didn't you? What about deprenyl?

GS: We never studied it definitively. It's a Hungarian drug and I heard somebody is developing a patch giving L-deprenyl. That would be very interesting, because you could give a high dose.

TB: Did you work with SSRIs?

GS: I used them widely, but I never was involved in any clinical trials. I wouldn't be surprised if venlafaxine is slightly superior to SSRI's, rather than the other way around.

TB: How do SSRIs, in your opinion, compare to imipramine or amitriptyline?

GS: There was an article in the *BMJ* not so long ago, saying that when they looked at amitriptyline, it was equal to or better than SSRI's and there was a follow up article that suggested less self-harm with amitriptyline than with the SSRIs. There are many fascinating findings in the antidepressant field. Clearly the advantage of SSRIs is thought to be safety. There was a study from somewhere around Detroit, in the mid 1950s, claiming that isoniazid has antidepressant effects. Now, isoniazid is a similar structure to iproniazid but does not affect monoamine oxidase. That would be interesting to look at.

TB: The isoniazid findings would invalidate some of the neuropharmacological speculations. Were the findings followed up?

GS: No but they are still using isoniazid in tuberculosis; that is something one still could look at.

TB: It seems those findings were overlooked. I wonder why?

GS: Imagine taking a Marxist from Russia in Stalin's days and trying to convince him that

Marx was wrong. Data aren't terribly important in belief systems, so that may be why those findings with isoniazid were overlooked. But, it's certainly of historical interest. David Healy raised the issue and I spoke to him about it.

TB: David raised the issue in his book, *The Antidepressant Era*.

GS: Yes.

TB: The findings with reserpine and iproniazid had a major impact on the development of neuropsychopharmacology.

GS: In the 1970's, a psychiatrist came to my office, closed the door and looked around in case anyone was listening, and then asked if I felt convinced that antidepressants worked.

TB: It took about eight years to show that they are effective. It was Klerman and Cole, about eight years after the introduction of imipramine, who first conclusively demonstrated that.

GS: Yes and Karl Rickels wrote about the effects of nonspecific factors on treatment. It's fascinating what expectation can do. This is where placebos come in; to eliminate all the noise that comes with the improvement you get in the first week in inpatients and outpatients with depression. The problem is that many places around the world, as for example Japan, do not allow the use of placebo in studies on depression. I think that's true in Europe now as well.

TB: In most of the studies with antidepressants, there is about a 30 to 35% response to placebo against a 65 to 70% response to the active drug. That is a real concern.

GS: I think that is a huge concern. At the same time, another reason for the problem might be in diagnostic practices, and I'm also a bit cynical about commercial testing. If I'm testing a drug and my living is dependent on the income, I put more patients into the study, whether I'm doing it consciously or not. A study I didn't mention yet, which I thought was one of the best we did, was a controlled inpatient study of 300 mg of imipramine vs. 150 mg. We had about 49 subjects and I think 47 out of 50 scale items showed greater improvement on the 300 mg. The WHO dose is still 150 mg as the upper limit. We had some psychotic depressions in that study. We obtained a 65% response rate for the non-psychotics and about 50% percent for the psychotics. So, I've always believed that many psychotic depressions take longer to treat and the idea they don't respond to antidepressants may not be totally valid. If you read Slater's biography, hospitals had many patients who were psychotically depressed and physicians had to tube feed them and we certainly don't see this any longer.

TB: Didn't you also study trimipramine?

GS: We looked at trimipramine because it was similar to methotrimeprazine.

TB: Weren't you first to report on trimipramine in the United States?

GS: Right. I looked at it at Rockland and it's very similar to levopromazine and drugs used widely in the treatment of psychosis. So, we looked at patients with schizophrenia but didn't see any antipsychotic effect.

TB: You also did some research with MAOI and tricyclic combinations.

GS: Right. I still feel that a combination of a tricyclic and MAOI is safer than a MAOI alone. There's a good pharmacological explanation for that based on animal studies and some human studies, including our own. Tom Cooper did some work in animals and when he gave them MAOIs and then tyramine, their blood pressure shut off. But if you pretreated them with tricyclics it didn't. Probably, the combination was more efficacious in treatment but nobody ever studied it adequately. I used nortriptyline plus a monoamine oxidase inhibitor. I would give nortriptyline at bedtime, because it appeared to help with sleep. It is one of those things that have remained controversial. If you're talking about treatment resistant depression, that's something you might want to do.

TB: Do you think that we have made progress in the treatment of depression with antidepressants?

GS: We've made progress in safety. If my life depended on treating someone who was depressed, I would not use an SSRI. An advance would be that it's more difficult to kill yourself with SSRI's and that is significant. This reminds me of Jonathon Cole saying that a consultant psychopharmacologist went around and increased the dose of tricyclic antidepressants and decreased the dose of antipsychotics. The big advance would not be for psychiatrists, so much, but for non-psychiatrists; family practitioners used 75 mg of imipramine and because of side effects never titrated to a full therapeutic dose; now they can give SSRIs starting with a full dosage in the majority of people. It was a smart marketing ploy by Lilly to go after nonpsychiatrists with these newer drugs. Only about 25% of psychotropics in the United States are prescribed by psychiatrists. At the same time, the societal benefit would be that perhaps more people get treatment than before, because tricyclic antidepressants were more difficult to use. The studies comparing them are very few and the Danish cooperative study certainly showed that clomipramine was superior to

fluoxetine; and I would bet none have shown the reverse. I also think nobody is going to show fluoxetine less efficacious than other SSRI's. That is something we should bear in mind.

TB: What about drugs like mirtazapine or trazodone?

GS: It's difficult to prove anything more than that they have been shown different from placebo. I know very few psychiatrists who use trazodone, except maybe at bedtime for insomnia. I think mirtazapine and trazodone are effective drugs, but what their place might be still needs to be defined. Bupropion is used increasingly because it does not cause sexual dysfunction like the SSRI's.

TB: What do you think about ECT?

GS: Most psychopharmacologists would say ECT is probably the most effective treatment for depression, and it certainly got bad press that was partly deserved. The late Bob Kellner, who was a member of the ACNP, used to say of some colleagues that the only indication for ECT was the presence of a patient. That's what gave it a bad press, but for severely suicidal, psychotic depression, catatonic symptoms it's an excellent treatment. I was very happy to hear on public radio, Kay Jamieson talking to a very good interviewer, who suggested psychotherapy for depression. She said, unfortunately the kind of depression I have, only responds to electrical treatment. The public is beginning to hear that and there are also articles talking about this. It's wonderful that some well-known people have come forward and talked about their own depression, even some who have had ECT.

TB: So your first choice in depression is ECT?

GS: I would use it as a first choice in psychotic depression.

TB: We talked about your research with lithium earlier. Are you using lithium in treatment refractory depression?

GS: Yes. Lithium is a rarely used drug in our department because when valproate came, they sold it to everybody saying it was the most efficacious treatment for bipolar patients, which is clearly untrue. It's never been proven; the more serious studies suggest lithium is still the drug to beat and I would agree with that. I also think that the side effects of lithium are somewhat exaggerated. For some patients it can be problematic, but we exaggerate it. I think there's a good database to contradict the statement that lithium does not work for rapid cyclers or mixed states. It certainly helped the famous patient in England with 48 hours cycles. It's hard to think of more rapid cycling

than that. We should be careful to teach findings based on group statistics because individuals can behave differently. Regardless of the symptomatology, I still start any bipolar patients with lithium.

TB: What about carbamazepine?

GS: It's all but disappeared from use and that's probably because you need to monitor it like you need to monitor valproate and it also has sedative side effects. But most importantly, it is not approved by the FDA for bipolar disorders and so it cannot be advertised like valproate. We are getting all of these other anticonvulsants, some of which work, and some of which do not.

TB: What is your first choice among the antidepressant drugs? Nortriptyline?

GS: Nortriptyline would be fine, but it would depend on drug history.

TB: What would be your first choice drug in schizophrenia?

GS: All things being equal, I'd probably start with an atypical, and the only reason would be to avoid EPS. There is evidence to support that. On the other hand, I think that low dose typical neuroleptics work quite well and while they do produce EPS, they can be minimized.

TB: Did you do any research with benzodiazepines?

GS: Not really. We did some pharmacokinetic work, but never a lot. I have a fellow doing a benzodiazepine withdrawal study in patients with panic disorder. They are on an SSRI plus benzodiazepine, so we are trying to withdraw the benzodiazepines. I did a little bit in panic disorder but I worked mainly in schizophrenia and depression.

TB: Did you look at the effect of antidepressants in panic disorder?

GS: We started to look at nortriptyline in panic disorder, when Ed Pi was in Philadelphia, with the notion that if blood levels were useful in depression with nortriptyline, perhaps, it would be the same in panic disorder. We started a preliminary study, but Dr. Pi returned to California and we never completed it. Mostly the populations I had were inpatients with depression or schizophrenia, and even the outpatients in the private sector, when I worked in New York were predominantly depression.

TB: What about treatment of dementia?

GS: I've really never done research in dementia. We did a study with an antipsychotic in elderly schizophrenic patients but we were mainly concerned about blood levels and not with dementia.

TB: Let's try to review your activities chronologically. You did one year of residency, in Montreal, then you moved to Rockland State.

GS: To Rockland, yes.

TB: You completed your residency there?

GS: Yes.

TB: How long were you at Rockland?

GS: Twenty years. I came to North America for a year and wanted to go back to London. I kept on postponing it, but I never gave up the idea. It just sort of disappeared. I remember going to see Aubrey Lewis, in New York, but he told me they were only taking people who had boards in Internal Medicine before they went into Psychiatry. That didn't exactly encourage me to go back, so I stayed on, met my wife, and that was that. It was comfortable at Rockland, since it was a big research environment. I mentioned Tom Cooper and Gene Laska, who made my life easier. That part of my life was fun and it just sort of unfolded.

TB: Why did you decide to leave?

GS: I decided to leave Rockland and New York, because we needed an acute population to do clinical research. I thought we had set it up but it didn't work out. So I decided maybe it's time for me to change. I came out to California because Bruce Sloan was the Chair and there had been problems at a local state hospital that involved some sudden deaths, so the state funded a Clinical Psychopharmacology Laboratory unit. I came out to set that up. We did a couple of studies, but the medical director for the state got fired and the new person did not support a public hospital academic liaison. We wrote a couple of papers while I was there. One was on, "the Therapeutic Advantages of Research," in which we described our findings with a group of patients we took off drugs for a week, and nearly all of them improved. It brought up the fact that even patients with schizophrenia improve in a nice environment. That was done probably in 1978 and 1979 and published in 1980.

TB: It was also about that time you published on, "Sudden Deaths in Schizophrenia."

GS: That was a Task Force Report for the APA. There was a lot of talk in New York State in those years because of a series of sudden deaths in patients receiving haloperidol. So, the APA convened a task force, which I chaired. I suspect there have always been sudden deaths in people with schizophrenia, and nearly everybody was getting haloperidol in those years. It could be related to

high dosages because studies in England showed that there's a dose response effect on the EKG, related to QTc. Haloperidol at 10 mg is probably fine, but if you keep increasing the dosage to a 100 mg, you get an effect. The APA report was inconclusive because there was no way at that time you could prove it, unless you did a huge post-marketing study. I suspect the introduction of psychotropic drugs cut the death rate in hospitals substantially, but within the total population there might be one or two people who had a sudden death that was drug related.

TB: You moved from Rockland State to L.A. and from L.A. to Philadelphia.

GS: Wagner Bridger, after he took the Chair at MCP in Philadelphia, had a goal of setting up a research team and invited me to come. When I asked, "to do what?" he said, "Whatever you want." I felt that was a nice offer, so I went and we did quite a lot of interesting work, like the "Treatment Strategy Study in Schizophrenia" that showed again, that low dosages didn't do badly. They had more threatened relapses, but we didn't have more hospitalizations. It also showed that a psychoeducational program was as good as a very complicated behavioral intervention. We did some of our clozapine studies; a study in which we compared different doses of fluphenazine; and we looked at moclobamide in panic and depression.

TB: Where did you do the clozapine withdrawal study?

GS: It was done at Rockland. We withdrew it abruptly and had a lot of problems: nausea, delirium, and a huge upsurge in abnormal movements. After that, we did the study in people who had tardive dyskinesia; we showed that clozapine suppressed or at least improved it. We tried abrupt withdrawal again and again saw delirium, a huge upsurge of movements, and nausea. Clozapine is probably the only antipsychotic drug I wouldn't withdraw abruptly, unless I absolutely had to, in a case of white cell suppression. We even suggested that the withdrawal effects were cholinergic phenomena. Our conclusion of that 1978 study included most of what we know about clozapine; that it doesn't produce EPS, it helps TD, can produce seizures, withdrawal effects, and helps patients who did not respond to other antipsychotics.

TB: We started talking about the research you did in Philadelphia. Is there anything else you would like to add from that period?

GS: We did studies on smoking in schizophrenia. These were sort of epidemiological studies, which showed a high rate of smoking in patients with schizophrenia. We did studies on water intoxication in schizophrenia with Jose de Leon and Cherin Verghese, and we looked at possible

interventions, for example with clozapine. We did studies with a young German medical student who had developed a technique for measuring facial movements, so we looked at TD with his technique. And I did a lot of teaching and met a lot of fine people who I still keep in touch and work with.

TB: When did you move from L.A. to Philadelphia, and when did you move back from Philadelphia to California?

GS: I came back to Philadelphia, in 1984, and left in 1994. We kept the house in the country in southern California and spent time there over holidays, and eventually, decided we would retire there. Some two months later, I got a phone call asking me to take a teaching research position at USC. I still had an NIH grant running in Philadelphia, so I had to commute there and back for a while. Then, I started to set up clinical research. There was no research in schizophrenia there. We have now a small research group in schizophrenia, and research is going on in depression in adolescents and in PTSD in adolescents and adults. That's been fun and interesting.

TB: You've had NIMH grants since the late 1950's. Could you tell us something about the different grants you've had?

GS: After the ECDU grant, we had grants for our blood level studies and developing our scales for EPS and TD. We also had quite a bit of funding from pharmaceutical houses for all of these studies. When I went to California, that was a state supported research unit which took a couple of years to get up and running, but as soon as it was up, the state had a change in leadership. So I went back to Philadelphia for nine years. Then, we had the Treatment Strategy study that was NIMH funded and the Clozapine Dose Response study, which went on for about six years. We also had grants for blood level study for fluphenazine. When I came back to California, and accepted the job offer my feeling was that I would work for a year or two setting things up and then disappear onto the golf course, but I kept on. We hadn't put in any NIMH grants because of my concern that I needed somebody, who would not only do the work, but be there to complete it. So, we're getting close to that stage now.

TB: You have interacted with the pharmaceutical industry for several decades?

GS: It was much more casual and intimate in the early years, but over time it evolved, like industry itself. It's become more and more difficult; it's hard to keep up with people. The industry has many people and they all seem to move around a lot; but now, it's much bigger and everything is more

complicated. There are multi-center studies but they do not allow any piggyback study that might interfere with the main study. Companies have become much more focused because the FDA has been more scrutinizing. So, if you ask what I think about it, I can't say I'm happy. Do I know how it could have evolved differently? I'm not too sure because the pharmaceutical company is there to make money and that was probably always true. Of course, there is this influence in the whole of medicine; the marketing techniques are questionable for some. That seems to be escalating.

TB: You have been at least on one NIMH committee I know of.

GS: I was on the Treatment Assessment Group at NIMH and I chaired it for a couple of years. It was a good education. Mike Goldstein was on that committee and he was a very superior, objective person, so I learned a lot from him. He knew what was happening in the field. Then I did site visits and those sorts of things, which were time consuming but interesting.

TB: Is there anyone who had a major impact on your professional development?

GS: A few people in Montreal like Bruce Sloane and my encounters with Heinz Lehmann. I think you are aware that he made one of his typical statements—that nobody who only spoke English could ever understand existentialism, so I stopped trying, and that saved me a lot of time. Then he taught me a most helpful thing, the need to change models in treating patients in different phases of their illness; he was really an excellent clinician and teacher. At Rockland, I never saw Nate teach, but I heard him give lectures. Eventually, I'd say I learned from nearly everyone in the ECDU because they were friends; although we did much the same things, each of us had his own area of interest. That was a very useful group. Gene Laska and Hillary Lee, who worked with me, both knew far more about statistics, data management, and handling, and taught me in that area. They were not formal mentors, but I learned from people who were around me or just by seeing patients.

TB: Would you like to mention any of the people you collaborated with?

GS: Philip May; we met through the ACNP, became friendly, and then worked on chapters for Freedman and Kaplan.

TB: What were the chapters on?

GS: "The Treatment of Schizophrenia." It was nice to work with somebody who was stimulating and I learned from him many things. I collaborated with Bob Kellner, because he was somebody I met in the anatomy department at Liverpool, who became a very close friend. I guess he, Philip

May, and Don Gallant were the closest friends I had in this country. I used to meet Bob Kellner at the ACNP and maybe one other meeting and we occasionally visited, but if he'd hear a good joke, he would always phone me. We used his depression scale in our imipramine study. I worked with Don Gallant in a Depression Symposium in New Orleans. Then, I worked a bit with Jonas Dencker in Goteborg.

TB: Would you like to mention by name a few people who worked with you or you trained?

GS: I had Scott Angus working with me and then he went to Canada and still lives there. Poddy Harper and Mark Branchey worked with me. Then, Guy Edwards came for a couple of years. I collaborated and worked with Doug Levinson and Ira Katz, who are now at Penn. Alan Bellack was a bright psychologist and he worked with me on the Treatment Strategies study; he's now in Baltimore. Jose de Leon worked with me for a couple of years as a fellow, published quite a bit, and still goes on publishing. He's now in Kentucky.

TB: You are a member of many organizations. Weren't you the first president of the American Society of Clinical Neuropsychopharmacology?

GS: No, I was one of the small groups of people who were concerned about clinical psychopharmacology. The idea was to have an organization that would help to get information about clinical psychopharmacology to practitioners. Gerry Klerman and Don Klein called a meeting in Washington, where this organization was born. I see this as an educational arm to the science organization. The new organization had something like 100 members, and I don't know whether it has had an impact on clinical practice or not, but that was the intent there.

TB: When did you become a member of the ACNP?

GS: In the mid 1960's. It was Nate Kline who suggested I should apply for membership. It was easy to become a member relative to today. I became a member and the meetings were unique, because you got a chance to meet nearly everybody. At a meeting like the APA, you have to search out people, and if you want to talk to them, you probably have to have lunch or dinner. At the ACNP, you could have a half an hour by the pool. So, you got to see and meet a lot of people in the field who were doing different things.

TB: You were president of the ACNP?

GS: Yes, in 1991. I served on the Council for three years, then I was president elect, and finally I was president. It was a good experience. There are some things that the ACNP is engaged in that are unique and novel, but others, I don't know how productive they are.

TB: Like what?

GS: Like going to Washington and up on the hill, to bring to the floor the sort of needs in science and our own field. You know as well as I do, it's a very unique organization.

TB: Would you like to mention any other organizations you are a member of?

GS: The APA, the Society of Biological Psychiatry, and the Royal College of Psychiatrists.

TB: Are you still working full time?

GS: Yes, I am.

TB: What would you consider your most important contribution in the field? You created the Simpson-Angus Extrapyramidal Symptom Rating Scale(EPS).

GS: That was useful for us at that time. You have people who have blinding insights and make advances, and you also need a group who do the tidying up work, which is important. I think I helped advance clinical practice by doing some of those small things. The imipramine study was important because it was one of the first that made any comment about the effectiveness of tricyclic antidepressants in psychotic depression, although that question is still open. It showed that you may need higher dosage. All of our works on side effects, withdrawal effects were important.

TB: You were also the first author of the TD scale.

GS: That developed in the midst of controversy about TD. First, we had an overinclusive scale, but then shortened it. We had the intention of examining postmortem the basal ganglia of patients who had TD vs. patients who did not, but that did not work out.

TB: You are a recipient of several awards. Would you like to mention some of the distinctions you received?

GS: In Philadelphia, I got the Alfred Noyes award for a body of work in schizophrenia. I got the Heinz Lehmann award and that pleased me a lot, since he had been a teacher and mentor. I got an honorary degree from the University of Goteborg for work that made a contribution to the field and had collaborated with people at that university. That was good; I had dinner with Jonas Dencker, Arvid Carlsson, and Gottfries, all distinguished people, Arvid being the most distinguished.

TB: How many papers did you publish?

GS: Probably 300.

TB: Would you like to say something about one or another?

GS: I like what I wrote on "Neuroleptic Malignant Syndrome." It's a practical guide to how to avoid and how to treat it. TB: What about books?

GS: I've written a lot of chapters in books, but the others were more like booklets. I was on the original task force on *Tardive Dyskinesia*, so our report was a monograph, and another short monograph was on *Sudden Death*. That's about what I've done. Even writing book chapters, I've tried to avoid.

TB: You've witnessed forty years of psychopharmacology. What are your thoughts about the changes?

GS: Mostly I feel positive. We have proven drug treatments, even though they may not be as efficacious as we would like, can make a huge change. When I went to Rockland, in 1958, and worked at a local mental health clinic, I had a man with panic disorder who, occasionally when it happened, would get out of his cab and wouldn't cross the George Washington Bridge. I was told by my supervisor he was suffering from homosexual panic. I talked to a friend in England and asked if I should give him a monoamine oxidase inhibitor. He said, sure, and I did that, and the homosexual panic went away. It was also dramatic to see some of the depressed patients free from their symptoms. No matter what anyone says, these are dramatic changes. In schizophrenia, there were no drug treatments until the antipsychotics came along. Progress in the treatment of schizophrenia has been disappointing because we have not made any giant leap forward after chlorpromazine. Then in mania, in severe bipolar illness, I used to give prophylactic or maintenance ECT, but after lithium came along, I did not need to do this very often.

TB: Are you pleased with the direction the field is moving?

GS: I cannot be displeased. The whole neuroscience component is a big plus. Imaging and genetics are exciting for psychiatry. There is no payoff as yet, but there will be. It's easy to focus on these new methods and underestimate the value of clinical contributions. To do a good clinical job takes a long time and it's not certain that you will be rewarded. But if you don't spend the time, all the high science in the world just creates confusion.

TB: What would you like to see happen in the future in psychiatry and psychopharmacology?

GS: I would like to see the genetic links to all the major illnesses. I think we are some way from that, but the technology seems to be there. I can see where nosology might get in our way because we can see in schizophrenia a group of illnesses; it creates problems if we treat them as one entity and lump them together in imaging or genetic studies. Yet, there is no easy way to separate schizophrenia into clinical groups. I don't know whether biological markers might mean we can attack the problem from the other way around. I would like to see more potent and rapidly working antidepressants, and in terms of anxiety, we could probably get a better drug, although I think we do reasonably well there.

TB: On this note, we should conclude this interview with George Simpson. Thank you, George, for sharing this information with us.

GS: Thank you.

60. LOUIS SOKOLOFF

TB: This will be an interview with Dr. Louis Sokoloff⁶² for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College in San Juan. It is December 8, 2003. I am Thomas Ban. I think we should start from the beginning. If you could tell us where and when you were born, something about your education and so on?

LS: I was born, in 1921, in Philadelphia, one of two sons of immigrant parents. We grew up in the 1920s. It was the Great Depression, a very bad period. My father was a working man, and there was always a problem of finding a job. It was also a time of intensive union organization and there were frequent strikes, during which he could not work. The depression years were, consequently, very formative in establishing my attitudes and viewpoints. I think, that probably, its impact on me made me a liberal for life. We didn't have much money for fun, and so I spent much of my time in reading. The public library system in Philadelphia was quite good, and I used it constantly to take out books.

My brother was six years older than I, and he had a big impact on my interests. He was academically inclined and had always wanted to be a physician, but we did not know if we would ever be able to afford the tuition for higher education. When, however, he graduated high school, in 1933, he won a scholarship to the University of Pennsylvania. While there, he majored in zoology, and I, probably because of that, also developed an interest in zoology. My brother lived at home during his college years and had all his textbooks there. I would read them and learned a pretty fair amount of zoology before I even got to college, myself.

The depression did have some beneficial effects on our educational system. The faculties in the Philadelphia public high school system were quite excellent at that time because, I suppose, many of the teachers had previously been on university faculties. Many universities, the University of Pennsylvania included, were closing down departments to save money, and so there were former faculty members who needed jobs. Some of them might have chosen to transfer from the

⁶² Louis Sokoloff was born in Philadelphia, Pennsylvania, in 1921. He received his M.D. from the University of Pennsylvania. After military service, he returned to post-doctoral studies, and subsequently, the faculty of the Department of Physiology at the University of Pennsylvania in Philadelphia. Thereafter, he was recruited to the Intramural Research Program of the National Institutes of Health in Bethesda, Maryland where he stayed for the remainder of his scientific career. He was interviewed in San Juan, Puerto Rico on December 8, 2003.

universities because of higher salaries, at that time, in the Philadelphia high schools. Therefore, a number of the teachers, perhaps, as many as half in my high school, were Ph.D.s. They were generally excellent and very stimulating teachers. I knew that I would be unable to afford to go to college, unless I also got a scholarship. Fortunately, I managed to do so by graduating first in my class in high school. At that time, the person who graduated first in his class was granted a 4-year scholarship to the University of Pennsylvania.

TB: When did you start college?

LS: In September 1939, just a couple of weeks after World War II had begun in Europe; I began my studies at the University of Pennsylvania with the intention of majoring in zoology. The College of Arts and Science in the University had, at that time, a liberal arts and sciences program, in which the first two years were largely defined or prescribed. As I remember, the requirements included three semesters of English composition, one each on the history of the English language and English literature, and also choices of courses in the physical and social sciences. Majors were chosen at the end of the second year. In my first year, the science courses I chose were General Zoology and General Inorganic Chemistry, and in my second year, Qualitative and Quantitative Analytic Chemistry, and Organic Chemistry. I found that I really liked chemistry, but my heart was still set on biology. Penn, at that time, had separate departments of Botany and Zoology, and although I was mainly interested in animal biology, I also took a couple of courses in botany.

When the time came for me to choose a major, my brother, who by then had had six years of prior experience, advised me and convinced the family that I should not major in zoology. Because we were still in a time of depression, he thought that I should choose chemistry rather than zoology as my major, because there were then few jobs for zoologists but greater employment opportunities for chemists. At that time, the Atlantic Refining Company and Sunoco Oil Company were located in Philadelphia, and these oil companies were still occasionally hiring chemists. I stubbornly resisted his advice, but did compromise by choosing zoology as my major, but also taking as electives, all the courses required of chemistry majors.

By the time of my third year, the United States was also in the war. Although I was eligible for the military draft, I was granted a deferment because I was a potential medical student, and premedical and medical students were then being deferred. It was during this schoolyear that I took a mixed graduate-undergraduate course called General Physiology, but it was really cell

biology. This course was taught by an outstanding cell biologist, Louis Victor Heilbrunn. He was, to my knowledge, the first one, certainly then the most vociferous one, to propose a key role for calcium in a variety of physiological and cellular processes, such as blood clotting, muscle contraction, regulation of protoplasmic viscosity in cells, membrane integrity and permeability, and cellular excitability. He argued that excitation in cells was associated with increased intracellular free ionic calcium concentrations, derived from increased membrane transport and/or release from bound stores. Much of this is now accepted as true, but he was then ahead of his time and considered by many to be too obsessed with calcium. This was a two-semester course with both laboratory work and lectures. In the first half of each of the semesters, we had assigned laboratory experiments, essentially exercises, that we had to do, and then, in the second half of the semesters, we were required to carry out an original research project. My research project in the first semester was to determine if the flow of protoplasm in the pseudopod of the amoeba obeyed Poiseuille's Law. I found that it did not. In the second semester, my research project, mutually agreed upon by Heilbrunn, Dan Harris, one of his senior graduate students and teaching assistants, and myself was to fractionate cells into their subcellular components and identify enzymes localized in each of the fractions. For a variety of reasons, mainly because the project was part of a teaching course and not supported by any research grant, we had to choose a cell type that was cheap, readily available, and relatively pure. For that reason, we chose the frog egg because it met all of the above criteria. By using differential centrifugation, we separated from the homogenized cells, cytosol (called plasmasol at that time), pigment granules, lipid fraction, and yolk, and found lipases in the lipid fraction and dipeptidases in the cytosol. I don't recall what enzymes we looked for and found in the yolk. This was in 1942, a couple of years before Schneider and Hogeboom reported their fractionation of cells into much more interesting subcellular components, for example, mitochondria, microsomes, and cytosol. I guess you can say we missed the boat, but the project certainly stimulated my interests in biochemical and biophysical aspects of cell biology.

This experience led me to enroll, during my last year, in an elective course called Undergraduate Research in Zoology, which allowed me to carry out further research under Heilbrunn. Because the United States was then at war, Heilbrunn had switched his research activities to a defense related project supported by an army grant. This project was to study the effects of heat on tissues. The army was interested in this research because of the numerous-heat-

related casualties that the British 8th Army in North Africa was suffering. Heilbrunn's entire staff, post-doctoral fellows, and graduate and undergraduate students were all working on various aspects of the effects of heat in tissues. My assignment was to use the rat sciatic nerve/gastrocnemius preparation, to determine the relative sensitivities of nerve and muscle to heat. The preparation was dissected out, and either the nerve or the muscle was submersed in Ringer's solution at 42°C. The nerve and muscle were alternately stimulated electrically, and the muscle contractions were detected by means of a mechanical lever and smoked drum. The stimulations were continued until muscle contractions ceased, and the time for this to occur was recorded. We found that the nerve was quite resistant to the heat and could be heated for quite some time before it failed to transmit the stimulation signal to the muscle. In contrast, when the muscle was in the heated bath, muscle contraction elicited by nerve stimulation was rapidly lost, but was maintained considerably longer in response to direct muscle stimulation. This indicated that it was the myoneural junction that was the most vulnerable component of the preparation to heat. Heilbrunn considered this observation sufficiently interesting to merit publication. I began to work on a manuscript at a desk located in an office I shared with Paul LeFevre, who was then a graduate student of Heilbrunn's, and later became well known for his work on red cell permeability. One day, as I was working on the manuscript, he told me that he had run across a paper that might interest me. Indeed, it did. It was a chapter written in French, in 1870, by Claude Bernard in a book, *Dictionnaire de Physiologie*, edited by Charles Richet. Claude Bernard had carried out almost the identical experiments that we had, except that he had used oil instead of Ringer's solution, and he obtained the same results, and drew the same conclusions as we did. I guess the culture of science then was somewhat different than from what it is today; it was a time when quality of publications rather than their number was what counted. Even though Bernard had done the work and published it more than 70 years previously, Heilbrunn acknowledged that we had been scooped and decided not to publish our results because someone else had already published the same findings and conclusions.

Because of my experience in Heilbrunn's laboratory, I became so fascinated with laboratory research that I asked him if he would accept me as a graduate student to work for a Ph.D. in zoology. He said, yes, he would be willing to accept me, but advised me not to do that. His reason was that because of the war, he was having trouble keeping his graduate students from

the military draft. He advised me instead, to go to medical school, which would allow me to be deferred until I finished medical school. I also remember him saying that he generally did not care much for medical education, but, added, "Medical school doesn't necessarily spoil everybody for scientific research." He also said, "I'll write you a strong letter of recommendation, and when I write a letter that strong, the student is always accepted." He did write such a letter, and I was accepted into medical school at Penn. Because of the war, the medical school had adopted an accelerated program, and therefore, my classes began at an odd time in March 1943. The accelerated program was designed for us to complete the normally 4 year's curriculum in three years. The purpose was to speed up the supply of physicians to meet the needs of the armed forces. The acceleration was achieved by having the courses immediately follow one another with no breaks and no holidays or vacations.

TB: You started medical school in 1943.

LS: Our first course in medical school was anatomy, and it made me think of quitting medical school. The atmosphere and my experience there was enormously different from what I had enjoyed so much while working in Heilbrunn's lab. There, we had been treated with respect as though we were mature scholars, whereas in the anatomy classes we were treated like kindergarten children. Everything was presented as an absolute fact, to be accepted and memorized. There were no dynamic processes to be analyzed, and no room for questioning or argument. Probably because of the war, however, I stuck it out, and subsequent courses in the first year turned out to be more interesting. It included physiology and biochemistry, both of which I enjoyed very much, as I also did pharmacology which followed.

About three months after starting my first year, the military took over the medical school. We were given the choice of joining either the army or the navy, provided, of course, that we could pass their physical examinations. We did have the option of not joining either, and anyone who chose not to, would be deferred from the draft until graduation. We were encouraged, however, to join because the military would then pay all the tuition fees and provide all the necessary textbooks and equipment. Those not joining, had to cover these expenses themselves. The tuition fee alone at that time was \$400 per year, which does not seem very much compared to those today, but it was a great deal at that time. My family's resources had been stretched very far by the payment for my first year, and I doubt that we could have afforded the costs till graduation. Joining the

military was, therefore, a great opportunity for me. Because my myopia disqualified me for the navy, I joined the army, in July 1943, and went through the remainder of my medical education while a private in the Army Specialized Training Program (ASTP).

All through medical school I found that I enjoyed the basic science courses most. These were physiology, biochemistry, and pharmacology. I suppose that I also enjoyed bacteriology and pathology, but not nearly as much. Although I was less interested in the clinical courses, I managed to do all right, and did graduate second in my class, in March 1946.

TB: What did you do after graduation?

LS: Immediately following my graduation from medical school, the army released me into the inactive reserves. This was a temporary arrangement, to allow me to complete an internship and obtain a license to practice medicine, after which they would recall me to active duty as a medical officer. I served my internship at the Philadelphia General Hospital (PGH), which doesn't exist anymore. It was a city hospital with 2,500 beds. The internship was a rotating one, which the state of Pennsylvania then required for licensing. My first rotation was in psychiatry. Subsequent rotations, not necessarily in that order, were in tuberculosis service, obstetrics, gynecology, laboratory medicine, internal medicine, orthopedic surgery, general surgery, neurology, and clinical pathology. Some of these rotations, such as obstetrics, were mandated by the state. Because the internship was also on an accelerated program during the war, it was compressed from its normal full year into nine months, during which we met all the required rotations. By that time, however, the war had ended, and it was decided in the midst of my internship to return to the one-year internship. In order to return to the normal July 1 to June 30 schedule, my class was given an extra six months, all to be served in only a single service. The service to which I was assigned was psychiatry. The transition from the nine-month to the full year old schedule resulted in several months of overlapping of a new group of interns with our class, during which the members of our class assumed duties and activities more like those of a resident than of an intern. During that period, I gained a lot of experience that included insulin shock and electroshock therapy. It was also a time when many physicians were returning from military service and were seeking advanced training in medical specialties, supported by the GI bill of rights. Philadelphia General Hospital had a very active psychiatric program with an almost unlimited supply of patients. It was housed in its own building, which contained about 300 beds for inpatients and very active outpatient

clinics. Furthermore, it was a teaching hospital with four psychiatric services, each chaired by a faculty member of the various medical schools in Philadelphia. Medical students from those schools served their rotations in psychiatry there. The PGH Division of Psychiatry, headed by John Stouffer, became a training center in psychiatry for physicians returning from the war, and our faculty included, among others, O. Spurgeon English from Temple University, Samuel Hadden from the University of Pennsylvania, and a Dr. Schlesinger, whose first name I cannot recall, from Jefferson Medical College. The training program included formal classes, lectures, and clinics, in which we interns and residents were allowed to participate. This greatly expanded our learning and experience beyond our practical experience in the wards and clinics, which was also quite considerable. In addition to his outpatient duties, each intern in the psychiatry service was responsible for two wards of approximately 40 beds each. The psychiatric services were very active with a large turnover, and we experienced and learned a great deal.

My internship ended in June 1947, and we were allowed a couple of months to take our state board licensing examinations after which the army recalled us to active duty. I reentered the army as a medical officer, in August 1947, and was first assigned to the Medical Field Service School, in Fort Sam Houston, Texas, for basic training that included, for example, setting up and operating battlefield aid stations, field hospitals, etc. After about a month of such training, we received our permanent assignments. To encourage us to choose permanent careers in the army, they sent a plane-load of brass from Washington to interview us about our preferences for specialty and place of assignment. We were allowed three choices for each. In keeping with my interest in the basic medical sciences, my first choice for specialty was physiology and specifically in the army's environmental physiology laboratory, located at Fort Knox, Tennessee. My second and third choices for specialty were internal medicine and neuropsychiatry. My second and third choices for places of assignment were Europe and California, in that order. In typical army fashion, they gave me none of my top choices and assigned me to Camp Lee, Virginia, as Chief of Neuropsychiatry in a 150-bed station hospital. My assignment to neuropsychiatry was undoubtedly due to my previous experience during internship and probably also because of the army's shortage of psychiatrists at that time.

TB: So this was in some way your third encounter with psychiatry.

LS: When I reported to Camp Lee, I found that there had not been a psychiatrist there for about six months. Their last one had completed his term of service and been discharged, and the army had been unable to find a replacement. In the interval, neuropsychiatry was covered by the medical service, which was very happy to see me come. When I arrived, I was given the option of keeping neuropsychiatry within the medical service or restoring it to its previous independent status. I chose to keep it within the medical service, so that I could maintain some contact with internal medicine, in which I was still interested, particularly metabolic disorders.

Although I did to participate in the care of patients in the medical service, most of my time was spent in neuropsychiatry. There were some neurological patients, but these were infrequent in subjects in the age group with which I was dealing. Most of the neurological conditions I saw were acute and most often due to injuries or sub-arachnoid hemorrhages, but I did see one case of a relatively rare and interesting condition, Thomsen's disease (myotonia congenita). I was also chief of the, so-called Psychiatric Consultation Service, which was responsible for evaluating all soldiers considered for court martial and those with behavior problems who were under consideration for discharge due to inability, inaptitude, or undesirable traits of character. Many of the latter fell into the category called at that time, "Constitutional Psychopathic Inferior," and now Sociopathic Personality. Most of my time, by far, was spent with psychiatric patients who covered the whole range of psychiatric disorders. These included psychoses, such as schizophrenia, but we did not have to treat psychotics. They were rapidly transferred to an army general hospital, usually Walter Reed. Consequently, most of my patients were neurotics. We were responsible for the care, not only of the military personnel, but also their families. This was fortunate because it gave me the opportunity to acquire experience with a greater variety of conditions and types of patients that included soldiers' wives and children. Patients voluntarily coming or referred to me, obviously needed help. What kind of help could a psychiatrist give them? Neuropsychopharmacology had not yet evolved. Psychiatry in the U.S., at that time, was largely dominated by psychoanalytic thinking. I had, of course, never really been trained as a psychoanalyst, but I had been extensively exposed to it during my internship and had read a great deal of the psychoanalytic literature. It seemed to me that it offered the best opportunity to provide effective psychotherapy to neurotic patients, and so I adopted a sort of a modified, or diluted, psychoanalytic approach to psychotherapy. Most of my psychiatric patients were outpatients. I usually saw them for an hour

twice a week during which they were allowed to freely associate and were interrupted only by an occasional question or comment of mine. One of my patients, the wife of a sergeant, had been referred to us by the medical clinic. She had been a patient of theirs for a long time, with a history of a variety of physical complaints, joint pains, headaches, gastrointestinal disturbances, chronic fatigue, etc., but they could never find any physical basis for them. They finally decided that she was a hypochondriac and referred her to me. I met with her twice weekly for an hour each time over a period of about six months.

Generally, I would begin each session with the question, "How have you been feeling since I last saw you?" I vividly remember the occasion when, after about six months of psychotherapy, her response to the question was, "Wonderful. I haven't felt this well in 13 years." I was flabbergasted. Although I had provided her psychotherapy, I really didn't have much faith in it. How did it happen? How could having her do most of the talking twice weekly for six months relieve her of all her physical complaints? Being strongly oriented toward the physical sciences and biology, I was sure that it had something to do with physiological or biochemical changes and, most likely, in the brain. To psychoanalysts, I suppose, this didn't matter. Leon Eisenberg, a medical school classmate of mine, has since become a prominent psychiatrist, and is now at Harvard. You may know him.

TB: Yes, I do.

L.S: This is a bit of a digression from my story, but, I believe an amusing one. Several years ago, Leon was invited to present a lecture to the Royal Society of Medicine or, perhaps, of Psychiatry, I don't recall which. This required a manuscript, and he sent me a draft of it. It was entitled, "Brainlessness and Mindlessness in Psychiatry." In it, he compared the state of psychiatry in earlier days, for example those days when I was in the army practicing psychiatry, when it was strongly influenced by psychoanalysis, and its present state. To psychoanalysts the brain was irrelevant. They were concerned only with the mind, whatever it might be and wherever it may have resided. Today, psychiatry is concerned mainly with physical elements within the brain, e.g., receptors, neurotransmitters, synapses, second messengers, genes, etc. Little thought is devoted to the mind per se. At any rate, even in those days, I had faith that psychiatric disorders, not only those associated with organic brain disease, but also the psychoses and neuroses, were diseases of the brain and had a biological basis. Of the functional disorders, this seemed to me to be particularly

true of schizophrenia. I had had several clinical experiences that tended to reinforce that belief. When I was at Philadelphia General Hospital, we saw many catatonic schizophrenics, whom, I understand, are relatively rare today. They frequently exhibited signs that suggested abnormal physiology. For example, I remember one catatonic patient who wouldn't eat, and we had to feed him by nasogastric tube. We would insert the tube through his nose, and when the tip reached his pharynx, we would squirt a little water through it to stimulate his swallowing reflex. He did not appear to resist, except on one occasion he contracted his nares so firmly that we could hardly move the tube in or out. That indicated extraordinarily strong muscle contractions beyond the range of normal physiological function and suggested that there was some neurophysiological alteration. Therefore, although I used a psychoanalytic approach for the treatment of my psychiatric patients, I always believed in biochemical or biophysical abnormalities in the brain as the cause of mental diseases. As a result of my experiences in psychiatry at Philadelphia General Hospital and in the army and my long interests in physiology and biochemistry, I began to consider seriously a career in which I might combine those interests in studies of the biology of mental disease, and that, of course, to me meant studying the brain.

The required duration of my army service, beginning in August 1947, was two years, and toward the end of 1948, I began to give serious thought about what I would do when I was discharged, in 1949. After all my time and experience in neuropsychiatry, an obvious choice would have been to serve a psychiatric residency and obtain board certification in psychiatry, and I gave this possibility serious consideration. I still, however, entertained thoughts of getting back to basic research, particularly on the brain. Sometime late in 1948, I ran across a series of papers by Seymour Kety and Carl Schmidt on the development and use of their nitrous oxide method for measuring cerebral blood flow and metabolism in man. I knew both of them from medical school. My class in medical school was Kety's first, after he joined Schmidt's Department of Pharmacology. I remembered him as a very kind, considerate, and supporting person and an excellent teacher, one not much older than we were. He was about six years older than I was, about the same age as my brother. In fact, Kety and my brother had attended Penn at the same time.

The nitrous oxide method measured the rates of the brain's blood flow, oxygen consumption, glucose utilization, and use or production of any other substrates and metabolic products that could be assayed in blood, and it did this in unanesthetized man. A description of the

method and a number of its applications were reported in a series of, I believe, six papers published, in 1948, in a single issue of the *Journal of Clinical Investigation*. There was another one in the *American Journal of Psychiatry* on its use in schizophrenics. When I first saw these papers, I was immediately impressed by the potential of this method to be a powerful tool with which to study the human brain in health and disease, including psychiatric disorders, and that was something I really wanted to do. I wasn't entirely sure, however, and did not exclude the possibility of first serving a residency in psychiatry.

My parents were still living in Philadelphia, and so when I was discharged from the army in August 1949, my wife, whom I had married during my internship, and I returned to Philadelphia and lived with them while I was deciding what I was going to do. I did nothing for about two weeks, except to think about visiting Kety at Penn and inquiring about the possibility of working with him. Finally, I screwed up my courage and did so without making any prior appointment. I went directly to the office of the Department of Pharmacology in the Medical School building, where he had been located when I was a student there, and asked the secretary if I might be able to see him. She replied, "He's not here anymore. He's now in the Department of Physiology and Pharmacology in the Graduate School of Medicine, not in the School of Medicine." I knew that Penn had a Graduate School of Medicine, but I had never heard of its Department of Physiology and Pharmacology. I learned later that large numbers of physicians returning from military service were taking advantage of their eligibility for further education supported by the GI Bill of Rights to obtain such education at the Graduate School of Medicine. One of the School's programs led to a Ph.D. in Medical Sciences, and this program required further education in the basic sciences. The University, therefore, had established or expanded its basic science departments in the Graduate School of Medicine. There had previously been a small Department of Physiology, but it was expanded into the much larger Department of Physiology and Pharmacology with Julius Comroe as Chairman and Seymour Kety as a full professor, both of whom had previously been in Schmidt's Department of Pharmacology in the School of Medicine. The offices of the Department in the Graduate School were in the basement of the Medical School building, and I found my way down to his office where I asked Mrs. Sullivan, the Department's secretary, if I could see Dr. Kety. She told me that he was meeting with someone, but if I was willing to wait, she was sure that he would be able to see me soon. I agreed to wait and after about a half-hour was able to meet with

him. I explained to him the purpose of my visit, my interest in his work on cerebral blood flow and metabolism, and my desire to work with him. I explained that I was bringing no original research ideas of my own and that my goal was only to learn and to work in whatever projects he chose for me. He replied that he remembered me from medical school and would be willing to take a chance on me. He then added something which he later claimed not to remember, but which I do very clearly. It was that he had just been notified that his grant had been approved and would be funded, and that it included a salary for a still unfilled position. The position and its salary, however, were for someone with much more experience than mine. Nevertheless, he was willing to take a chance on me, but in view of my inexperience, at a lower salary. He then added that, perhaps, with the salary money left over, he could appoint another fellow like me. Very practical, I thought. His acceptance of me was conditional, however, on its approval by Dr. Comroe, the Department Chairman, who of course, would first have to interview me. I returned to Mrs. Sullivan to make an appointment for such an interview and obtained one for two weeks later.

There was an amusing sidelight associated with this interview. While I was standing in the hall waiting to see Kety, Comroe had walked by and, seeing me, asked if I were waiting to see him. At that time, I was not yet aware that he was the chairman of the department, and so I said no, I wanted to see Dr. Kety. When I arrived for the interview with him two weeks later, the first thing he said was, "So you thought you could get away without seeing me." What a way to begin! I thought that was the end, but when I explained to him why I was there, he replied that he also remembered me from medical school and would approve the appointment. He then asked what my plans were for the future. I was surprised by the question and replied that my plan was, I thought, obvious. It was to come to work for Dr. Kety. He explained that he meant my long range plans for the future. Was I coming with the intention to make a career in physiology or, since I had a medical degree, was I coming to spend a year or so in laboratory research before returning to clinical medicine? My reply was that I did not know. I knew only that I had always liked basic science, but since I was just about to begin doing research in basic science, I did not yet know if I would prove suited for a research career in physiology. His response was that he remembered me from medical school, was confident that I would do well in research, and hoped that I would decide to make a career in physiology. I was flattered and pleased to hear that, but then he added, "But not here." I was surprised and asked what had I said or done wrong for him to have already decided

that. He explained that there were between 20 and 30 members of the Department, but only three of them were on university salaries, himself, Seymour Kety, and Mrs. Sullivan. "I am 38-years-old and in good health, and not planning to leave," he continued, "Kety is 35-years-old, and, as far as I know, also in good health and not planning to leave, and so you cannot replace either of us. And as for Mrs. Sullivan, the secretary, and I don't think you could do her job." He then added, "You are coming here to help us do our research. In return we will teach you how to do research. And if and when you learn enough to be able to do your own research, we'll help you find a place to do it, but somewhere else."

In those days, NIH grants did not allow principal investigators any salary off their own grants. Maybe you remember those days. That was the basis of Comroe's statement that only three in the department were on university salaries. All the others were getting their salaries off Comroe's and Kety's grants. When any of those became independent enough to get their own grants and wished to remain in the department, their salaries would then have to come from the university, and such salaried positions were not readily available. When I understood this, his statement seemed reasonable, and not a criticism of me, and I accepted the position.

It turned out to be a wonderful choice and a great experience. The department was outstanding, arguably the best physiology department in the country, at that time. I learned a great deal from Kety and Comroe and from many of the others in the department. One important and lasting lesson was to be completely rigorous and to be as critical of one's own work, as of that of others. We learned in our weekly seminars that every statement we made had to be backed up by relevant and substantive facts or reasoning, or else we were subjected to strenuous questioning and criticisms. I was indeed very fortunate and happy to have been trained there.

TB: When did you join the department?

LS: I joined the department in the fall of 1949. Sometime late in 1950, I believe, a couple of men in white uniforms, which we thought were naval officer uniforms came to see Kety. His office had two doors, one in front opening into the hallway and the other a side door that opened into a large room where all the research fellows had desks. The latter door was almost always open, and we would often go into his office and bother him, or else he would come out and talk with us. He seemed to like to be interrupted and to interact with us. On this occasion that door was closed, and the two uniformed men spent nearly all day with him in his office. Finally, they left, and the door

opened. All of us research fellows were keenly interested because we knew that if the navy wanted something from Kety, it was likely to impact on us. We asked Kety what the navy wanted, and he corrected us that they were not naval officers but Public Health Service officers. One was Bob Felix, then the Director of the newly established National Institute of Mental Health (NIMH). You knew him I suppose.

TB: Yes, I do.

LS: The other one was Joe Bobbitt, the Executive Officer of the NIMH. We asked Kety what they wanted, and he informed us that they came to offer him the position of Scientific Director of this new institute and of the also newly created but smaller National Institute of Neurological Diseases and Blindness (NINDB). His responsibility would be to direct the intramural research programs of both institutes. When we expressed our doubts that he, a full professor in a prestigious Ivy League university and in an excellent department with a very supportive Chairman, would be interested in such an offer, he surprised us by saying that he had always been interested in mental health and considered the offered position a great challenge to do something worthwhile in the field. He would have almost unlimited space, budget, and positions with which to create from scratch a formidable research program in neuroscience. The challenge of creating such a program appealed to him, and he would not reject it out of hand. We then asked why they would want him, a physiologist with little, if any, training and experience in psychiatry, to develop and head a program in mental health research. He replied that that was a good question that he himself had asked of them. Their answer had been that that was exactly why they had selected him. They thought that a scientific director of a major research program on mental and neurological diseases should be a basic scientist, and not a psychiatrist or neurologist.

TB: They wanted a basic scientist.

LS: Kety had received great acclaim and recognition for his development of the nitrous oxide method for measuring cerebral blood flow and metabolism in man and was at the top of his career. He was naturally reluctant to give this up and enter into essentially a new career, and he spent several months agonizing about the offer and consulting others for their advice. Finally, he decided against most advice to accept the offer, and he moved from Penn to the NIH, I believe, late in the summer of 1951.

TB: What about you?

LS: I stayed on at Penn. By then, I had become his most senior post-doctoral fellow and continued the research for which Kety had received his two NIH grants. Because NIH policy at that time would have prevented me from receiving any salary from those grants if I became principal investigator, Comroe assumed the role of principal investigator of Kety's grants and allowed me to continue working on them. The department had two main areas of research directed by Kety and Comroe. Kety's domain was cerebral blood flow and metabolism and peripheral circulation. Comroe's was respiratory physiology. It was an outstanding department. The pulmonary physiology program under Comroe was arguably the finest in the world, as was also the cerebral blood flow and metabolism program under Kety. Richard Wechsler, who later went into internal medicine and gastroenterology, was Kety's first post-doctoral fellow, and I was his second. We were, subsequently, joined by Renward Mangold from Bern, Switzerland, who also later became a gastroenterologist; Charles Kennedy, a pediatrician who later became the first person to be boarded in both pediatrics and neurology; Benton King and Eugene Connors, anesthesiologists; Jerome Kleinerman, who also later went into internal medicine; and Reuben Copperman, a graduate student in biophysics, from whom I learned a great deal of mathematics. It was a smooth working and very collegial team, while it lasted. Kety, of course, had been the magnet that attracted and could assemble such a team. After he left, no one new came, and the team disintegrated. I was left with Copperman and a technician. Those of us who remained were still happy with our own research, but the atmosphere became somewhat boring because we did not have a critical mass within our area of interest, with whom to converse and exchange stimulating ideas. Comroe's pulmonary physiologists did not have much interest in cerebral circulation and metabolism, and we had little interest in their field.

The U.S. Navy had the Naval Air Development Center in Johnsville, Pennsylvania, just outside of Philadelphia. They had established there the Aviation Medical Acceleration Laboratory, where they wanted to study the physiological bases for blackout and red-out in pilots undergoing gravitational stresses during plane maneuvers. This facility was equipped with a centrifuge that had a 50-foot arm and a gondola at the end with which they could subject animals and people to gravitational forces comparable to those encountered by pilots during plane maneuvers. It was hypothesized, but not proven, that blackout was due to inadequate perfusion of the brain, and they appointed me as a consultant to assist in the development of a method to

measure cerebral blood flow and metabolism during imposed gravitational stresses in that centrifuge. I generally went out to Johnsville once or twice a week to participate in experiments designed to develop such a method. After a couple or so years of that, they decided to offer me the position of head of their physiology laboratory. Because of my feelings of isolation in the department at Penn, I decided to accept their offer and went to Comroe to tell him of my decision. He did not want me to leave, especially to go work for the Navy, and asked me to remain in his department and join the group working in pulmonary physiology. I explained to him that lung function might be interesting to some, but I did not find it particularly stimulating and wanted to pursue my interests in cerebral blood flow and metabolism. He then called Kety at NIH to tell him that I wanted to leave the department and suggested that he offer me a position rather than let me go to the Navy. Kety then called me to offer me a position and explained that he had not done so previously because he had not wanted to rob the department at Penn. Since, however, I was leaving anyway, why not come to NIH? I accepted his offer.

TB: What year are we in?

LS: This was in 1953. I signed in sometime in December 1953 but did not really begin to work there until early in 1954 because the laboratories were not yet ready. In the interim, I continued working at Penn. When I finally arrived, Kety was working on the development of a method for measuring blood flow locally in the different parts of the brain. There was indeed need for such a method. The nitrous oxide method, which measured only average rates of blood flow and metabolism in the brain as whole, had shown only reductions in cerebral oxygen consumption in states in which consciousness was impaired. It had failed, however, to show any increases in any conditions and also did not detect any changes in a variety of physiological, pharmacological, and pathophysiological conditions in which cerebral functional activities must certainly have been altered. For example, it showed no changes in cerebral oxygen consumption in subjects during performance of mental arithmetic, slow wave sleep, hyperthyroidism, sedation, inebriation, etc. Cerebral oxygen consumption was also found to be unchanged in schizophrenia which led Kety to jest that, perhaps, it took just as much energy to think an irrational thought as a rational thought. These results led to speculations about why cerebral energy metabolism appeared to be unaltered during obvious changes in brain function. A popular belief at the time was that cerebral energy metabolism was already operating at its maximal rate, which could be reduced by conditions that

impaired consciousness but could not be detectably raised by increased functional activity in the brain. The brain was compared to a radio in which most of the energy is used in the filaments to heat the cathodes of the vacuum tubes but is negligibly altered by the signals or information being transmitted, whether it was music, speech, or static. We, however, did not believe that. Our hypothesis was that the nitrous oxide method failed to show increases in energy metabolism during functional activation because it measured only the average in the whole brain, while specific functional activities are localized to specific regions of the brain. What was needed was a method that measured energy metabolism in the individual regions of the brain. Furthermore, it had to be a method that could be applied without the need for general anesthesia, which itself is likely to alter brain functional activity. Kety initiated a project to develop such a method shortly after he arrived at NIH. He was assisted by William Landau and Walter Freygang, both Research Associates in the Laboratory of Neurophysiology, NIMH, and Lewis Rowland, a Clinical Associate in the NINDB; and I joined this group when I arrived. At that time, it was not obvious how one might approach the question of how to measure local energy metabolism in the brains of un-anesthetized, behaving animals. Kety's previous research on the principles of inert gas exchange between blood and tissues had led, however, to a possible approach to the determination of local cerebral blood flow. Blood flow in the brain, was thought to be adjusted to metabolic demand. This approach proved successful. We succeeded in developing the first method for determination of the rates of blood flow locally in every region of the brain of unanesthetized animals. The method was based on the uptake from blood to brain of a chemically inert, radioactive gas, ^{131}I -labeled trifluoriodomethane ($\text{CF}_3[^{131}\text{I}]$), and it took advantage of a unique quantitative autoradiographic technique that made possible the measurement of the local concentrations of the tracer within the brain tissues. With this method, we were able to measure the rates of blood flow in all parts of the brain in conscious and thiopental-anesthetized cats and found that anesthesia reduced blood flow in all gray matter structures, but particularly in sensory cortical regions, which, I suppose, is the main purpose of using general anesthesia. We also used the method to demonstrate that local blood flow does change in brain regions with normal alterations in functional activity. For example, retinal stimulation with a photoflash was found to increase blood flow in all stations of the primary visual pathways in the cat, and these changes were clearly visualized in the autoradiograms. This was the first demonstration of functional brain imaging. It should be noted

that although the blood flow techniques was originally developed for use with the ^{131}I -labeled gas CF_3I and autoradiography, it was later adapted for use with the non-volatile ^{14}C -labeled tracer iodoantipyrine and autoradiography in animals and with ^{15}O -labeled water and positron emission tomography (PET) in man.

TB: Have you been involved in any other project at the time?

LS: There were also other projects, in which I was involved after my arrival. For example, I set up the nitrous oxide method for measuring cerebral blood flow and metabolism in man and used it in studies of the effects of LSD and of normal aging. My main interests, however, were in metabolism which required knowledge of biochemistry. Although I had learned a lot of biochemistry from textbooks and reading of the literature, I had had relatively little biochemical laboratory experience. It turned out that NIH was a wonderful place to remedy this deficiency, because we were all mixed together, biochemists, physiologists, pharmacologists, anatomists, etc. In fact, when I first arrived, I was in the Laboratory of Neurochemistry, which contained, in addition to my Section on Cerebral Metabolism, the Section on Lipid Biochemistry and the Section on Physical Chemistry. I was surrounded by biochemists and joined a biochemical journal club. There I met Seymour Kaufman, an outstanding enzymologist, who later distinguished himself by his work on the mechanisms of amino acid hydroxylation, for example, phenylalanine hydroxylation to tyrosine, dopamine hydroxylation to norepinephrine, and tryptophan hydroxylation to hydroxytryptophan, all reactions important to neurotransmitter syntheses.

In earlier studies at Penn with the nitrous oxide method, we had found cerebral oxygen consumption to be entirely normal in adult patients with hyperthyroidism, in whom, total body oxygen consumption was increased by 50-70%. I became interested in the question of what was different about brain energy metabolism compared to that of other tissues that made it unresponsive to thyroid hormones. It soon became obvious, however, that to answer that question one would have to know the mechanism by which thyroid hormones stimulated energy metabolism in responsive tissues. From exhaustive examination of the literature, I arrived at the hypothesis that thyroid hormones primarily stimulated protein synthesis but had little if any effect in mature brain because its rate of protein turnover is so very low compared to that of carbohydrates metabolism. I presented this hypothesis and the evidence in favor of it at a session of the biochemical journal club. It turned out that Seymour Kaufman had arrived at the same hypothesis,

but from a different direction. We decided to collaborate on a project to examine this hypothesis. It was a fortunate collaboration for me, because it was obvious that testing of the hypothesis would require mainly biochemical experiments, and though I had always been interested in biochemistry and had acquired a pretty fair knowledge of biochemistry from book reading, I had had relatively little experience in its laboratory techniques. It turned out to be a very fruitful collaboration. We complemented each other. Kaufman was an outstanding biochemist and enzymologist who came from a background in organic chemistry, while I came from a background in physiology and medicine. He was a stern and rigorous teacher, who over a period of years trained me in practical as well as theoretical biochemistry and made me a biochemist. I became so intrigued by the power of biochemistry to arrive at definitive conclusions that I remained fully engaged in it for at least the next 20 years. Incidentally, we did find that thyroid hormones do, indeed, stimulate protein synthesis in those tissues in which they stimulate oxygen consumption and published this finding first as a preliminary note in *Science*, in 1959 and then in more complete form in the *Journal of Biological Chemistry*, in 1961. Although my laboratory work during those years was largely in vitro biochemistry, I never lost my interest in cerebral metabolism and the possibility of using the quantitative autoradiographic technique developed for the local blood flow method to measure local cerebral energy metabolism. Autoradiography requires, of course, the use of a radioactive tracer. Of the two almost exclusive substrates of the brain's energy metabolism, oxygen and glucose, oxygen was impractical because the half-life of its radioactive isotope, ^{15}O , is only two minutes. Glucose labeled with ^{14}C was a possible alternative because its rate of utilization in brain is stoichiometrically related to that of oxygen. I tried to develop such a method for use with ^{14}C glucose shortly after the local blood flow method had been developed. My first step was to try to design a kinetic model for the behavior of ^{14}C -glucose in brain that would define the variables and parameters needed to be known in order to compute the rate of glucose utilization from measurements of radioactivity in blood and/or plasma and the cerebral tissues. I dropped this effort, when I realized that ^{14}C -glucose metabolism to $^{14}\text{CO}_2$ in brain and the removal of the $^{14}\text{CO}_2$ from the brain by the cerebral circulation are so rapid that it was impossible to estimate the amount of product derived from ^{14}C -glucose utilization over a given interval of time. In 1957, I was writing a chapter for the *Handbook of Physiology* on the metabolism of the central nervous system in vivo and was working on the part in which I was arguing that glucose is not only the preferred substrate

for the brain's energy metabolism, but actually an essential one. The evidence was that insulin-induced hypoglycemia leads to loss of consciousness, slowing of the EEG, and markedly reduced cerebral oxygen consumption, and that when the blood glucose level is restored by glucose administration, all these changes are reversed. I was looking for additional evidence that the effects of insulin-induced hypoglycemia on brain functions were due to lack of glucose and not to the insulin per se. I was discussing this issue with Don Tower, a neurochemist in the NINDB. He told me about still unpublished studies that were being carried out by Bernie Landau in the National Cancer Institute, in which he was finding that the administration of pharmacologic doses of 2-deoxyglucose, an analogue of glucose, produced a clinical state just like that of insulin induced hypoglycemia, but in the presence of an elevated blood glucose concentration. The animals lost consciousness, just like in insulin-induced hypoglycemia. Apparently 2-deoxyglucose was interfering somehow with glucose metabolism in the brain. This was the kind of evidence that I was looking for, and I cited Landau's work in my chapter as a personal communication. I remained curious, however, about the mechanism of its effects in brain. How did it produce coma? It was likely to be competing with glucose, but the dose that produced coma did not appear to be large enough for the 2-deoxyglucose to compete with the much higher blood glucose levels to the point that blood-brain transport of glucose was insufficient to maintain cerebral glucose utilization and consciousness. It was known from the earlier studies of Sols and Crane that 2-deoxyglucose was a substrate for hexokinase and could compete with glucose for phosphorylation in the glycolytic pathway. Normally, however, there is plenty of glucose in the brain, and furthermore, hexokinase has a much greater affinity for glucose than for 2-deoxyglucose. It was unlikely, therefore, that competitive inhibition of glucose phosphorylation was sufficient to produce coma. There must have been some other explanation, but what was it? I didn't do anything about it except to follow the growing literature on the effects of 2-deoxyglucose. Finally, a publication by Wick, Drury, and others appeared which showed that it was not 2-deoxyglucose itself but its phosphorylated product, 2-deoxyglucose-6-phosphate that blocked glucose metabolism. The mechanism appeared to be as follows. Glucose-6-phosphate, the product of the hexokinase-catalyzed phosphorylation of glucose, is normally rapidly isomerized to fructose-6-phosphate, which is then metabolized further down the glycolytic pathway and eventually into the tricarboxylic acid pathway. In contrast, 2-deoxyglucose-6-phosphate lacks the oxygen on its 2-carbon position and cannot,

therefore, be converted to fructose-6-phosphate and metabolized further. Therefore, because the brain has very little if any hexose-6-phosphatase activity, 2-deoxyglucose-6-phosphate accumulates in brain to levels that exceed that of glucose-6-phosphate and inhibits glucose-6-phosphate conversion to fructose-6-phosphate. This effectively blocks glycolysis and glucose utilization in the brain and is responsible for the coma. When I saw this paper, I immediately thought that this property of 2-deoxyglucose might offer a means to use the quantitative autoradiographic technique to determine local rates of glucose utilization in the brain. 2-Deoxyglucose is an analogue of glucose that crosses the blood-brain barrier and is metabolized in the brain in competition with glucose in the first step of glucose metabolism, but then its metabolic product, unlike those of glucose metabolism, is essentially trapped and accumulates in the brain. It seemed to me that this unique property should allow one to determine how much 2-deoxyglucose had been phosphorylated and from that one should be able to figure out some way to compute the rate of glucose utilization. To do so would, however, require some type of kinetic modeling and analysis that was not immediately obvious. I was at the time still deeply involved in the studies of the action of thyroid hormones on protein synthesis, and so I set this idea aside as something for me to work on some day.

TB: You did return to it. So, when did you return to it?

LS: In 1964, Martin Reivich, who was serving his required two years of military service as a Research Associate in the U.S. Public Health Service, at NIH, joined our lab. He had previously been trained in neurology at the University of Pennsylvania and came to work with Seymour Kety and me on cerebral blood flow. At that time, neither Kety, nor I was working any longer on cerebral blood flow; Seymour had become involved in biochemical and genetic studies of schizophrenia, and I was working on the thyroid project. Both of us, however, had always had an interest in adapting the old autoradiographic [^{131}I]-trifluoriodomethane gas method for use with a non-volatile, long-lived ^{14}C -labeled tracer because of the greater convenience and better autoradiographic resolution it offered. Reivich did just that while he was here. He succeeded in adapting the local blood flow method for use with [^{14}C]-antipyrine, and in doing so, he also modified the quantitative autoradiographic technique for use with ^{14}C instead of ^{131}I . Quantitative autoradiography with ^{14}C was, of course, an essential step toward the development of a method to measure local cerebral glucose utilization with 2- [^{14}C]-deoxyglucose. We discussed this further

application of ^{14}C autoradiography and agreed that someday we ought to do something about it, but not then. In 1966, Reivich returned to the Neurology Department at Penn. Shortly thereafter, he called me to ask if he could include in a grant application he was preparing a section on the development of the ^{14}C -deoxyglucose method, and if I would be willing to collaborate with him in such a project. I agreed on condition that the initial experimental work would be done in his lab, because mine was then totally occupied with biochemical studies of the action of thyroid hormones and the cerebral utilization of ketone bodies. The initial studies done in his lab showed that 2- ^{14}C -deoxyglucose and glucose were taken up from the medium by brain slices in vitro in almost exact proportion. This encouraged us to develop a model for their behavior in brain in vivo. The model was essentially the same as the one for the measurement of local cerebral blood flow with a chemically inert radioactive tracer, such as ^{131}I -trifluoriodomethane or ^{14}C -antipyrine, except that it included a trapping step to account for deoxyglucose phosphorylation by hexokinase. The model was not wrong, but it led to a technically impractical if not impossible procedure that would have required simultaneous measurement of local blood flow and knowledge of some parameters that were extremely difficult to determine.

In 1968, I was presented with the opportunity to take a sabbatical year to work somewhere else. I realized that it might be my last chance to do that, and so I decided to go for a year to the Laboratory of General and Comparative Biochemistry, in the College de France, Paris, France. This laboratory, headed by Jean Roche, was then internationally renowned for its work on thyroid hormones. Professor Roche, who was then also the Rector of the University of Paris, was at that time fully occupied in dealing with a student body then in revolt, and the laboratory was essentially being run by Jacques Nunez. I collaborated with him on a project on the biosynthesis of thyroid hormones. A key step in the pathway of this synthesis is the iodination of tyrosine residues in the protein thyroglobulin in the thyroid gland. This reaction is normally catalyzed by the enzyme thyroid peroxidase. To study this peroxidase-catalyzed protein iodination reaction, we used a model system in which horse radish peroxidase was used to catalyze iodination of serum albumin. The kinetics of this reaction turned out to be peculiar. It did not follow typical Michaelis-Menten kinetics, which intrigued me. We did eventually find the explanation for the unusual kinetics. The reaction was a bimolecular one that required the sequential addition of two substrates, iodide and serum albumin, to the peroxidase enzyme. The order of addition was qualitatively random, but

there were kinetic preferences in the orders of addition, and simulation studies showed that the observed aberrant kinetic pattern could be duplicated, if appropriate rate constants in the various steps of the reaction sequence were used. One very fortunate outcome of working on this problem was that it taught me a great deal about enzyme kinetics. Furthermore, when the student revolt was over and they had returned to the university, I was incorporated into teaching a graduate class in biochemistry. The subject of my lectures was the regulation of enzyme activities. This experience further prepared me for what was to come. I began to think about the 2-deoxyglucose method more as an enzyme kinetic problem rather than as a blood flow and transport problem.

When I returned to my own laboratory at NIMH, in 1969, after spending my sabbatical year abroad, I found the thyroid project in shambles. I had the choice of trying to resurrect it, or to take the opportunity to use the enzyme kinetics I had learned and switch my lab's focus to work on the development of the deoxyglucose method. I chose the latter. After initial biochemical experiments with brain homogenates in vitro, we carried out our first experiment in vivo in which we injected ^{14}C -labeled deoxyglucose into a rat and autoradiographed its brain. This was done in February 1971. The development of the 2- ^{14}C -deoxyglucose method for the measurement of local cerebral glucose utilization in rats was completed by 1974, and by 1976, we had completed its adaptation for use in monkeys. It was subsequently adapted by us and by others for use in cats, dogs, mice, and sheep and fetal lambs.

TB: When did you move from animal research to man?

LS: After the autoradiographic 2- ^{14}C -deoxyglucose method was developed, Reivich, a collaborator in its development and a neurologist who necessarily dealt with human subjects, raised the question about the possibility of adapting it for use in humans. I remember quipping, "Sure, maybe one of the countries that still uses beheading as a penalty, would allow us to inject some ^{14}C -deoxyglucose into the subject before they beheaded him and then allow us to take the brain out for autoradiography. It's not very practical to do autoradiography on a human brain." He replied that maybe there was another way. He had met at the University of Pennsylvania David Kuhl, who was in nuclear medicine there, and had with his colleagues developed a single photon scanner that could scan the brain for γ -ray radiation and localize its distribution. It had four scintillation counters arranged in a rectangle in a plane that rotated around the head and could measure the radioactive emissions from localized regions in slices of the brain, one plane at a time.

They had used it, I believe, to measure local blood contents in different parts of the brain by using radioactive carbon monoxide which bound to hemoglobin. I acknowledged that the scanner might solve one problem but raised another. It required an isotope that emitted gamma-rays that could penetrate the brain and skull and be detected by the scanner outside the head. The problem was that deoxyglucose contains only carbon, hydrogen, and oxygen. There are no gamma-emitting isotopes of hydrogen; oxygen has one, ^{15}O , but with only a two-minute half-life; and carbon has ^{11}C , which has a 20-minute half-life. I didn't know how one could synthesize deoxyglucose, labeled with any one of these short-lived isotopes fast enough. What was there to do? Another possibility occurred to us. At the time, I belonged to a wine-tasting group at NIH, composed mainly of biochemists who met about once a month. One of its members was Peter Goldman, a biochemical pharmacologist, now at Harvard, who was then doing research on the biochemical properties of fluorinated analogues of natural compounds. Fortunately, I knew something about his work. He had, for example, shown that glutamate decarboxylase, the enzyme that makes GABA from glutamate, could also decarboxylate fluorinated glutamate to make fluoro-GABA. Fluorine is so small an atom that when it is inserted in place of a hydrogen in a not too critical position in a molecule, enzymes acting on the natural compound often act on the fluorinated compound, at least qualitatively, like on the natural compound. ^{18}F is a gamma-emitting isotope with a 110 minute half-life, long enough, perhaps, to permit synthesis of practical quantities of 2- ^{18}F -fluorodeoxyglucose. A further concern was where in the molecule to insert the fluorine atom to assure that the compound was still a substrate for the enzyme hexokinase. 2-Deoxyglucose has 6 carbon atoms, and it is phosphorylated by hexokinase on the carbon-6 position. The carbon furthest away from the phosphorylation site that could be fluorinated was carbon-2. It seemed, therefore, that the compound most likely to meet all the criteria was 2- ^{18}F -fluoro-2-deoxy-D-glucose (^{18}FDG). We were not, of course, radiochemists, and so Kuhl enlisted the aid of Alfred Wolf and Joanna Fowler, from Brookhaven National Laboratories. Reivich, Kuhl, Wolf, Fowler, and I, and some of their colleagues held a meeting in Philadelphia, where we discussed our need for ^{18}FDG . Wolf and Fowler were sure that they could synthesize it. I then insisted that they first synthesize a ^{14}C -labeled version of the species of fluorodeoxyglucose, so that we could do the biochemical and in vivo animal studies needed to confirm that the compound did indeed behave like 2-deoxyglucose. Kuhl and Fowler succeeded in doing that, and we used the ^{14}C -labeled FDG in enzyme assays and

animal studies to show that the proposed ^{18}F FDG would have the same biochemical properties as 2-deoxyglucose. Wolf, Fowler, and several of their colleagues also developed a synthesis for the ^{18}F -labeled FDG, and studies with ^{18}F FDG in human subjects were successfully carried out with Kuhl's Mark IV scanner at Penn, in 1976-1977. These were the first determinations of regional glucose utilization in the human brain. The images, however, were not very good, nowhere near those obtained with the autoradiographic technique. This was because the spatial resolution possible with the single photon emission scanner was in the range of centimeters, whereas that of the autoradiographic techniques was about 100-200 microns. Shortly thereafter, Kuhl left Penn to assume the role of Chief of Nuclear Medicine at UCLA. He took with him Michael Phelps and Edward Hoffman, who had been working with him at Penn but had previously been intimately involved in the design and development of the first positron emission tomographic (PET) scanners, when they were at Washington University. At UCLA, they acquired the first commercial PET scanner, the ECAT II. ^{18}F is a positron emitter, and its positron emissions are the source of the gamma rays that were exploited by Kuhl's single photon scanner. The positron, which has the same mass as the electron, is emitted from the atomic nucleus. It is absorbed in the tissue by collision with an electron in its environment, and the masses of both the electron and the positron are converted into two so-called annihilation gamma rays of equal energy. These gamma rays leave the site of the collision in opposite directions at approximately 180 degrees. Because gamma rays are less readily absorbed by tissue, they can be detected by radioactivity detectors outside the head. The gamma rays move in opposite directions with the speed of light, and so by having two detectors lined up which can measure the gamma rays arriving at them in coincidence, it is possible to localize the line in the tissue from which the rays originated. By having many such pairs of detectors around the head, it is possible to localize the region in the brain from which the two rays originated. Then, with the aid of computer images, the distribution of the radioactivity in slices of the brain can be constructed. This is, in brief, the principle of positron emission tomography. It provides much better resolution than single photon scanning, in the range, for example, of millimeters. This resolution is still far less than that of autoradiography, but PET does, after all, allow the measurements to be made in humans. Phelps, Hoffman, Kuhl, and a number of associates then proceeded to adapt the ^{18}F FDG technique for use with PET and applied it to humans in a variety of normal functional states and clinical conditions, among them normal aging, partial complex

epilepsy, Huntington's disease, Alzheimer's disease, and, more recently, neoplasms. These studies established the usefulness of the ^{18}F FDG method to study the human brain in health and disease.

TB: What was the time frame of these developments?

LS: The autoradiographic [^{14}C]-deoxyglucose method was first presented, in 1974, at the annual meeting of American Society for Neurochemistry. In 1975, we published in *Science* the first report of how it could be used for functional mapping, that is the mapping and imaging of functional activity in neural pathways. This report in *Science* did not, however, include quantification; it showed only how changes in functional activity could be visualized and localized in the autoradiographic images that the method provided. In 1976, we published in *PNAS*, its use to map functional activity in the primary binocular visual system in the monkey. This report included the visualization of the nature and extent of the ocular dominance columns in the primary visual cortex, as well as the localization, for the first time, of the site of representation of the blind spots of the visual fields in the visual cortex. In 1977, we published the full details of the theory, procedure, and applications of the quantitative deoxyglucose method in the *Journal of Neurochemistry*, and later that year, we published a short review of its many applications in the same journal.

The development of the ^{18}F FDG method for use in humans with the single photon scanner was essentially completed, in 1977, but it was not published until 1979, because of the many coauthors in different institutions, which had to be allowed to review and edit the manuscript. It was eventually published by Reivich and the rest of us in *Circulation Research*, at least a couple of years after its completion. The adaptation of the ^{18}F FDG method for use with PET, in which I collaborated, was also published in 1979, by Phelps et al. in the *Annals of Neurology*.

You might find it amusing to know why the full paper on the [^{14}C]-deoxyglucose method was not published until 1977, even though it had first been reported in abstract form in 1974. At the time, when we were working on the development of the method, I was the Chief Editor of the *Journal of Neurochemistry* and a very conscientious one. I had a rule that any submitted or revised paper received in the mail had to be sent out for review by the next day. Also, any reviews received from the referees would also be acted on by me by the next day and forwarded to the authors with a decision letter that was not a form letter, but one tailored specifically to that manuscript and its reviews. That was practically a full time job helping others to get their papers published, and it did

not leave me much time to write my own. At that time, I had a Japanese research fellow, my first Japanese fellow, Osamu Sakurada, who was part of the group working on the development of the deoxyglucose method. He had come from the Department of Neurosurgery of Juntendo University in Tokyo, and a friend of his from that same department was then also a fellow in Janet Passonneau's Laboratory of Neurochemistry, in the NINDS. Sometime in 1976, Sakurada asked me if there was something wrong with the deoxyglucose method. I was surprised and asked him, as he had been working with the method, had he found something wrong with it. He said that he himself didn't see anything wrong with it, but his friend had told him that at a journal club meeting in Dr. Passonneau's lab, she had remarked that there must be something wrong with the method because the abstract had been published in 1974, and yet the full paper had not yet come out. This alerted me to the possibility of a serious problem, and so I resigned as Chief Editor of the *Journal of Neurochemistry* and spent the next six months writing the paper. That is the story of why the full paper followed so long after the abstract.

TB: Now, in the 1980s, you continued.

LS: Yes, I continued working with the method, to a large extent on the effects of neuropharmacologic agents related to the various neurotransmitter systems. These included, for example, dopaminergic, serotonergic, adrenergic, and cholinergic systems. Some of the drugs we examined were amphetamine, apomorphine, haloperidol, LSD, phenoxybenzamine, propranolol, morphine, diazepam, phencyclidine, and ketamine.

We also worked on the sites and the mechanisms of activation of energy metabolism by neuronal functional activation. These studies definitively demonstrated the surprising fact that functional activation of a neural pathway stimulates glucose utilization in the neuropil, specifically in the regions of the synaptic terminals in the projection zones of the pathway, and not at all in the perikarya in the region of origin of the pathway. The perikarya do consume glucose, but it is probably used mainly for "house-keeping" functions, such as the synthesis of proteins, nucleic acids, and lipids, as well as axonal transport, etc. and is not altered by functional activity in the pathway. Furthermore, the increases in glucose utilization in the terminal zones of the activated pathway are linearly related to the spike frequency in the afferents to the synapses and is used mainly to supply the energy for the increased Na^+, K^+ -ATPase activity that is needed to restore the ion gradients across the membranes, which are partially degraded by the action potentials. An

interesting outcome of these findings was the explanation of why activating inhibitory pathway stimulated glucose utilization in its terminal zones is just the same as activation of an excitatory pathway. It was not because inhibition required energy just like excitation, as was often speculated. It was because it was the spike activity in the afferent terminals that was responsible for the change in energy metabolism, and this would be the same whether it resulted in release of an inhibitory or an excitatory neurotransmitter. To determine which neurotransmitter was being released, it would be necessary to look at the next synapses of the pathway.

TB: What about in the '90s?

LS: In the '90s, we returned, in part, to working on local cerebral blood flow. We were particularly interested in the physiological and/or biochemical mechanisms responsible for the increases in blood flow associated with increased functional and metabolic activities. We never did succeed in defining them, but we did make some interesting findings in the course of these studies. For example, we found that pharmacologic doses of 2-deoxyglucose or insulin-induced hypoglycemia of sufficient degree markedly increased blood flow everywhere in the brain. The glucose concentration in brain under normal normoglycemic conditions, for example, plasma glucose concentrations of about 7 millimolars, is between 2 and 3 millimolars, approximately 50 times the K_m of hexokinase for glucose. With progressively deeper levels of hypoglycemia, brain glucose concentration falls almost linearly with plasma glucose concentration, but cerebral glucose utilization remains more or less constant because hexokinase still remains relatively saturated over a wide range of cerebral glucose concentrations. In this range, cerebral blood flow also remains more or less constant. Eventually, however, when plasma glucose concentration falls into the range of 2-3 millimolars, cerebral glucose levels fall to levels around the K_m and hexokinase becomes unsaturated, causing cerebral glucose utilization to fall. Surprisingly, we found that despite the decrease in energy metabolism, cerebral blood flow was markedly increased, a complete dissociation between energy metabolism and blood flow in the brain. But why? Normally, cerebral blood flow is expected to be adjusted to metabolic demand. What in this case causes the blood flow to go up, when metabolic demand goes down? We spent a lot of time studying that. Our first thought was that nitric oxide might be involved, and that perhaps, it was formed or released by the reduced glucose utilization and was dilating the blood vessels. We, therefore, administered inhibitors of nitric oxide synthase. These did lower baseline cerebral blood flow but did not prevent

or even reduce the increase due to hypoglycemia. Our next thought was that, inasmuch as hypoglycemia is one of Cannon's four stress conditions, it was likely to cause the release of epinephrine and norepinephrine by the adrenals, and that their elevation in blood might be causing the increase in cerebral blood flow. To examine this possibility, we measured blood norepinephrine and epinephrine levels and found that they did, indeed, rise markedly in hypoglycemia. We then infused the catecholamines intravenously at rates that raised their blood levels to the same or even higher levels than those found in hypoglycemia, but that failed to alter either cerebral blood flow or glucose utilization. It could not, therefore, explain the blood flow response to hypoglycemia. We then considered the following scenario. When the brain glucose concentration falls to a level close to its K_m , hexokinase becomes partly desaturated, and the rates of glucose phosphorylation and utilization fall to rates insufficient to maintain normal rates of ATP synthesis. ATP levels then fall, while those of ADP and AMP rise. AMP is the substrate for 5'-nucleotidase, which dephosphorylates it generating adenosine. Adenosine is known to be a potent vasodilator, probably via its action on the adenosine A_{2a} receptor, and has been shown to be involved in the regulation of the coronary, and probably also, the cerebral circulation. To test this hypothesis, we measured brain adenosine levels during both insulin-induced hypoglycemia and after pharmacologic doses of 2deoxyglucose at the levels that increased cerebral blood flow. In both cases, brain adenosine concentrations were tremendously increased. We then reasoned that, if indeed, it was adenosine that mediated the increases in cerebral blood flow, then blocking adenosine receptors should also block the blood flow response. Since we had no idea about which of the adenosine receptors might be involved, we used a relatively non-specific antagonist, caffeine. Sure enough, caffeine dose-dependently inhibited the blood flow response to hypoglycemia, to the point of complete extinction. It was very gratifying to have a definitive answer to an interesting problem, and furthermore, it provided strong evidence that adenosine does indeed have a role in the control of the cerebral circulation.

TB: You are still active, right?

LS: I am still presently active, but my lab's personnel and resources have been reduced to the point where it has become very difficult to do the kind of work I used to be able to do. I am, therefore, planning to retire next summer.

TB: Next summer?

LS: Yes.

TB: What would you think was your most important contribution?

LS: I think that my most important research contributions were the development of the 2deoxyglucose method and using it to show that local brain energy metabolism can not only be measured, but that it can be exploited to localize neural functional activity, and even to image its distribution within the brain. In addition, we were able to use the method to define a number of the properties of the metabolic response to functional activation. For example, we showed that the changes in energy metabolism evoked by alterations in functional activity occur in the synaptic regions in the neuropil and not at all in the neuronal cell bodies. Furthermore, the change in the metabolic activity found in these regions in the neuropil, reflects mainly the change in spike frequency in the terminals of the afferent pathways to the region. I wish that those who use the ¹⁸FDG version of the method with PET would pay more attention to this point. When they find a region in the brain with altered metabolic activity or blood flow, they should not, as they unfortunately often do, necessarily conclude that that region is the site of the altered function. Altered metabolic activity in any given region may rather reflect altered function in regions upstream that project to it.

We also learned a great deal about the mechanisms that underly the functional activation of energy metabolism in the nervous system. These changes occur in the synaptic regions. Action potentials in the presynaptic axonal terminals and in the postsynaptic dendrites reflect sodium entry into and potassium exit from those cellular elements. These action potentials tend to degrade the ion gradients that generate the membrane potential and must be restored by pumping the sodium out of the cell and transporting potassium back into the cell. This is done by Na⁺,K⁺ATPase which consumes ATP in the process, and this requires glucose utilization to provide the energy needed to regenerate the ATP.

There are, in addition, some other processes that are associated with neuronal functional activity and are also dependent on energy metabolism. The increases in energy metabolism associated with functional activation of a pathway are localized to the neuropil containing the synapses to which the pathway projects. Neuropil contains several subcellular elements, such as presynaptic axonal terminals, postsynaptic dendrites, and astrocytic processes. The deoxyglucose method is not yet capable of the fine resolution required to identify which of these subcellular

elements contribute to the activated energy metabolism. Because action potentials in the axonal terminals and the dendrites degrade ion gradients, which must be restored, it is almost certain that these elements contribute to the increased energy metabolism. There are, however, studies with cell cultures in vitro carried out by Magistretti's group, as well as ours, that indicate that astroglia may also contribute to the functional activation of glucose utilization. Astrocytic processes surround the synapses, and astroglia have the property of avidly taking up glutamate, which is the most prevalent excitatory neurotransmitter in the brain and is released in the synapses of excitatory pathways. Glutamate uptake by astrocytes is associated with the co-transport into the cell of 2-3 sodium ions per glutamate molecule. This sodium must then be pumped out of the cell, and this is done by Na⁺,K⁺-ATPase which uses up one ATP molecule for every 3 sodium ions pumped out. The astroglia also convert glutamate to glutamine, a process that also uses one ATP molecule for each glutamate converted. The increase in energy metabolism observed with neuronal functional activation is, therefore, I believe, distributed among presynaptic axonal terminals, postsynaptic dendrites, and in glutamatergic synapses in the astrocytes with processes surrounding the synapses.

TB: So we should focus on the synaptic area to which the pathway projects, because this is where the activity is?

LS: Yes, and that is the reason I said that I wish those using the ¹⁸FDG method with PET would appreciate this. If they find a region with low metabolic rate, they should not conclude, as they often tend to do, that that is where the abnormality is. No, not necessarily. It may be that the problem is somewhere else, for example, the origin of a pathway that is projecting to this area.

TB: How would this translate into clinical interpretation of findings?

LS: I think the lesson is that in trying to localize the sites of abnormalities in disease or the actions of drugs, one should remember that what is observed in one area may well be a reflection of what happened somewhere else.

TB: Is there anything we did not cover?

LS: Well, there are probably a lot of things.

TB: But you think that we covered the important things?

LS: I think so. We got the most important things.

TB: When did you become a member of ACNP?

LS: I am not sure, but I believe it was some time in the 1970's.

TB: Have you been attending the annual meetings regularly?

LS: Oh, yes, I usually come to the meetings, at least two of every three years, and have participated in many sessions.

TB: What would you like to see to happen in your field in the future?

LS: I would like to see the biochemical abnormalities in schizophrenia identified. It won't, of course, be by me. I think that the imaging field is going to get better and better as the instrumentation gets better and better. It should be remembered, however, that one should not derive a functional model from what is imaged with PET or fMRI. The model should be designed from what is already known about the processes involved, and the images serve only to localize the process. For example, in the case of the deoxyglucose method, we first designed the model on the basis of known principles of enzymology and the results of basic biochemical and physiological studies in animals and man. All this was independent of, and preceded, any imaging techniques that were later used. The imaging techniques, first autoradiography, and then single photon emission tomography and PET, were added only to obtain localization of the metabolic process within the brain and played no part in the theoretical basis and design of the model. The fact that the imaging techniques allowed us to visualize the distribution and the levels of metabolic activities within the brain, and in colors of the rainbow too, was only a secondary gain. If, on the other hand, we had begun by injecting radioactive deoxyglucose and then examined the images, we wouldn't have had much of an idea about what was going on. If one were to inject radioactive shoe-polish and image the radioactivity in the brain, one would almost certainly find patterns of distribution of radioactivity in the brain which might change with functional activation. One would not, however, obtain from the images alone, any worthwhile information or useful knowledge about the nature of the processes involved, that would allow one to design a model. Just injecting a radioactive compound and getting an image is not enough. It must be combined with basic fundamental research beyond the imaging in order to get meaningful information from images.

TB: This is a reasonable note on which to end this interview.

LS: OK.

TB: Thank you very much for sharing all this information.

LS: Thank you. It's good to remind oneself of one's past.

61. A. ARTHUR SUGARMAN

TB: This is an interview with Dr. A. Arthur Sugarman⁶³ for the historical series on neuropsychopharmacology for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. We are at the annual meeting of the College in San Juan, Puerto Rico. It is December 9, 2002. Let's just start from the beginning. Where and when were you born? Tell us something about your education and just go on chronologically.

AS: As someone once said, I was born at a very early age. I was born way back, in 1929, in Dublin, Ireland, and grew up as the oldest of four children. I was back there recently on a couple of occasions. The place has certainly changed. I started at the Jewish National School in Dublin, the first such school that opened there. Church and state were not as clearly separated in Ireland as they are here today. There were Protestant schools, Catholic schools, and the one Jewish school. All were supported by the government, provided they taught the Irish language. Schools that did so, were given grants toward the school. I did quite well and went on a scholarship at a Methodist high school for four years, from 1942 to 1946. There again, I did very well, especially in mathematics. I again won a scholarship to Trinity College in mathematics. At that point, I had already decided to study medicine. I'm not quite sure why. I could have gone in for engineering, but medicine looked like a better career. I could have been a mathematician, a professor, I suppose. But, anyhow, in Dublin, as in many other British colleges, you take your university and medical degree at the same time. So I got my BA with honors, in 1950, and my medical degree, in 1952.

TB: What did you do after that?

AS: I did an internship, and since Ireland at that time produced more doctors, priests, nuns, nurses, and dentists than it needed for home consumption, I went to England. I did another internship in London and I was senior house physician at the Brook General Hospital in London. At that time, I was looking forward to doing internal medicine. It was 1953, when I arrived in London; the Queen had just been crowned. The decorations were still up. They had what they called the Festival of London. The city was very bright and gay, but the food was terrible, still rationed six years after the war. I looked around, and found during my work in internal medicine, that about half the

⁶³ A. Arthur Sugarman was born in Dublin, Ireland, in 1929. He received his medical degree from Trinity College in Dublin, Ireland. He was interviewed in San Juan, Puerto Rico on December 9, 2002. Sugarman died in 2007.

patients I saw had psychiatric problems. So I thought that might be the thing to do. I was offered a psychiatric residency in the Midlands, at Darby for six months full-time, and then, went to Sheffield, where Professor Martin Roth had just started his chairmanship. At the same time, Professor Erwin Stengel was nearby, in Sheffield, and I went to him for lectures. It was a small group. There were four or five of us in this particular program, one in each of the hospitals in the Sheffield region.

TB: So you did part of your training with Martin Roth?

AS: Yes. He was somewhat nervous taking over from Professor Alexander Kennedy, who was a very outgoing guy, while Martin was not. As you remember, he was rather reserved, quiet, not demonstrative, while Kennedy was the sort who would hypnotize the whole class to show how it was done. But Martin did quite well; he impressed the faculty of the Royal Victoria Infirmary at Newcastle, not by being a psychiatrist, but with his knowledge of neurology. He was called in to consult on cases; Martin had trained in neurology at National Hospital, Queen's Square, in London. Supposedly, he was able to diagnose a brain tumor others had missed in a psychiatric patient and that made his reputation. There were some very good people, e.g., Henry Miller, a neurologist, and John Walton, who later became Sir John Walton, and president of the BMA.

TB: Am I correct that we are in the mid 1950s?

AS: That was from 1955 to 1958. A few years later, Martin Roth had a textbook with Eliot Slater and Mayer-Gross.

TB: It was probably just about the time you arrived that Mayer-Gross moved from Newcastle to Birmingham.

AS: I think he was still in Scotland. It was an interesting and exciting time. We had six months of full-time study; the rest we spent in the hospitals.

TB: Was there any research going on?

AS: No. There was not much research going on, at that time. I really started with my research later. But I did get a pretty good training in psychiatry with some psychology and statistics. Eventually, at the end of that training, I took a Diploma in Psychological Medicine, at the Royal College in London.

TB: What did you do after that?

AS: I finished training and was looking around for what to do. Had I stayed in England, which it really was not the time to do, I would have had to put in time in Her Majesty's armed forces, which I was not too keen on doing. So, I accepted an offer from a member of a team of New Jersey medical directors, who were touring England and visited our hospitals. They came to see how the open door system worked after hearing how wards were unlocked in England; all their wards in the States, of course, were locked. Apparently, at that time, patients were used to taking orders from someone higher in rank; the British knew their place in the social system. So, if a doctor or a nurse told them to stay on the ward, even if the door was open, they obeyed the hierarchy, the pecking order. In America, if you opened the door and told them to stay in the ward, patients would head down the road as soon as your back was turned. In America, everybody is equal, and people don't take orders from anybody.

So, I headed for the U.S. and found myself in a large psychiatric hospital, in Trenton, NJ, where people were real friendly. I met some nice people, including my wife. I was there for a year, but then I accepted an offer of a research fellowship, in Brooklyn. The medical director at Trenton was very unhappy and wrote a letter of non-recommendation, saying I was not dynamic, meaning I didn't subscribe to psychoanalytic principles and the job should be given to an American, not a foreigner. In spite of that, the people who interviewed me, including Dave Engelhardt, were very nice and accepted me and three others for psychiatric research training. That was from 1959 to 1961. So, for a year, I was in Brooklyn, commuting weekends to Trenton to see my wife. We married in 1960, lived in Trenton and commuted in opposite directions because I was doing the fellowship in Brooklyn, and she was going for her master's in education in Philadelphia. As I said, I did a research fellowship with Dave Engelhardt. I was interested in Kretschmer's idea, and was testing the process-reactive distinction. I finished my fellowship in 1961; my thesis was on prognostic practices in schizophrenia, a developmental approach.

TB: Didn't you use perceptual tests?

AS: Yes, we did, and besides that, we looked at the whole process-reactive distinction in schizophrenia, and the premorbid history. Phillips was the man who developed a scale for distinguishing "process" from "reactive" schizophrenia using three criteria. Of course, all that is obsolete now, since DSM came out. What we were calling process schizophrenia is schizophrenia, and what we were calling reactive schizophrenia is diagnosed as an acute psychotic reaction.

TB: So this work was done in the early 1960s?

AS: This was in 1961 to 1962 and we published several papers on the findings. We were able to show in figure drawings that process schizophrenics had the poorest self-concept.

TB: Published when?

AS: In 1964.

TB: What did you do after that?

AS: I looked around for a job, preferably a research job, and there were none to be found. One other factor, of course, was that in New Jersey, at that time, you couldn't get a license without being a citizen. I couldn't get a license until 1963, so I had to find a job where I could work without a license and preferably do research. After several months of looking, I found that not too far away was the New Jersey Bureau of Research Neuropsychiatric Institute, where Joe Tobin was director of research. Remember Joe Tobin? He was one of the founders of the ACNP. So I visited and met not only Joe Tobin, but Carl Pfeiffer and Leo Goldstein, who was working in quantitative EEG. So I accepted the job and took over a unit of chronic schizophrenics. I also took over the drug studies that Joe Tobin had initiated and an ECDEU grant which had just begun. And that's how I fell into drug research and met up with several members of the ACNP. TB: By taking over the grant you became a member of the first ECDEU group?

AS: Yes. I started there, in 1961, and the ECDEU grant came immediately after.

TB: Could you tell us something about the research you did and papers published in those years?

AS: The first few papers had to do with the quantitative EEG research I was doing with Goldstein and Murphree in psychotic patients. LSD was popular at that time, and they were using it as a treatment for alcoholics.

TB: Did you do any work with Carl Pfeiffer?

AS: Yes, indeed. He was a very interesting man; he was also one of the founders of ACNP, in that first photograph with all the founders, at the original dinner. He is very recognizable with his close-cropped white hair. He had come to New Jersey from Illinois, where he had been professor of pharmacology and chairman of the department. I believe he brought Leo Goldstein with him from Illinois. Henry Murphree may have gone down to Emory from Illinois before he came to New Jersey. I know that Murphree graduated from Emory. Anyhow, he had a major heart attack before he came, and was looking for something quieter than university work.

TB: Was Pfeiffer involved in research with trace elements in those years?

AS: That came later. What they were really working on was the brain wave work, and he wanted to look into brain wave variations produced by different drugs. They were giving various drugs to normal subjects and looking at brain waves. But my involvement with them was with schizophrenic patients. Murpree went on to become a member of the faculty of the medical school that is now the Robert Wood Johnson Medical School. When it started, it was Rutgers Medical School and he became chairman of psychiatry. Murpree was also a very interesting man, since he'd had training in pharmacology but didn't have training in psychiatry until he went to Rutgers, where he moved quickly up to become chairman of the department. He is now retired. And, of course, Leo Goldstein was a lovely man. He had come from France and had great ideas about what to do. He was always better at getting the EEG results he wanted than I was. I used a similar apparatus and a sound proof room to duplicate his work, but I never really succeeded. His results were eventually replicated at several labs in Europe and eventually, in the United States. Unfortunately, the method was too simple and you just couldn't get a federal grant. Max Fink got the federal grants. I visited Max and was very impressed with what I saw. He had a lot of support from the state of Missouri, as well as from the federal government.

TB: You were in charge of chronic schizophrenics. How many patients did you have?

AS: Well, we generally had about forty. So, we were doing mainly small studies. You know, 6, 8, 10, 12 patients.

TB: Did you always use clinical and electrophysiological measures?

AS: Yes, at the beginning. Later on we used primarily the BPRS and the NOSIE. We were one of the first to use the NOSIE.

TB: Didn't you study some of Paul Janssen's drugs?

AS: Yes. I worked with haloperidol and later with fluoropipamide. He called it pipamperone.

TB: It was the one he thought has a kind of atypical neuroleptic effect.

AS: True, it did have some atypical effects, but then I thought molindone did also. You know molindone made the patients happier. It didn't cause weight gain or lactation. But that has been largely ignored, unfortunately, and people haven't paid much attention to it. There were many other antipsychotics at that time; it was about the end of the phenothiazine era and the beginning

of the butyrophenone era. I also did the first study in this country with pimozide, and with half a dozen thioxanthenes, most of which have not been released for clinical use.

TB: Did you work with thiothixene?

AS: Yes, but that was a Pfizer compound.

TB: Could you talk about your ECDEU grant? You were involved with ECDEU from early on. Can you recall who the other EDCEU investigators were?

AS: That was a very exciting time. Interesting people were involved, and we all got together, as you recall, for very pleasant meetings, generally at some other investigator's base, so we had an opportunity to see where others were working. There was a heavy concentration of people from New York, Nate Kline and George Simpson from Rockland; Hy Denber from Manhattan State; Sid Merlis from Central Islip; Arnie Friedhoff from NYU. Don Gallant was there from New Orleans.

TB: And Mel Bishop.

AS: Bishop, yes. Al Kurland was there from Maryland. He was also one of the early ECDEU investigators.

TB: Max Fink?

AS: Yes, Max Fink.

TB: Dave Engelhardt?

AS: Yes, Dave Engelhart from Brooklyn, and, of course, yourself and Heinz Lehmann from Canada.

TB: Pierre Deniker?

AS: Yes, Pierre Deniker. We had meetings in a variety of places; first it was only the investigators. Then the drug companies found out about it, and sent representatives; it became hard to have meetings of the investigators without the drug companies. In the beginning, we had a chance to present our results to each other first. That was a very interesting time, when you saw how other people dealt with the drugs you had been testing. We found, for instance, that experience is very important in using rating scales; people, who had seen a wide range of pathology, rated differently from people, who had only seen a narrow range. We showed that psychiatrists and psychologists rated the same way. I remember going to Palo Alto for an ECDEU meeting, as well as a meeting in New Orleans. Don Gallant took us for dinner at Antoine's. Oh, we forgot Burt Schiele.

TB: Burt Schiele played an important role in the beginning.

AS: Doug Goldman was also there, involved with the VA.

TB: For how long did you have the ECDEU grant?

AS: I had my ECDEU grant from 1961 to 1972 and after 1972 I think all the ECDEU grants faded away. They were not renewed after that. I was able to do some studies outside of my unit in the state hospital and other facilities. I did a study with haloperidol in geriatric patients at a state supported hospice, in New Jersey. I remember studying benzodiazepines on an "addictions unit." There was a study with prazepam and placebo in the treatment of convalescing narcotic addicts, in 1971. So, all that stopped in 1972.

TB: What did you do after your ECDEU grants expired?

AS: By that time, the state of New Jersey, like other states, had lost interest in supporting drug research. It happened in the other states, too. And when the grant expired, there wasn't much future in doing clinical studies. What happened was that Pete Penick, who participated in a VANIMH study of lithium at the Carrier Clinic, decided he wanted to do a residency in psychiatry.

So he asked me to take over that study from him and I went to work part time at the Carrier Clinic. Then, Dr. Carrier asked me to join the clinical staff of the Clinic. And after that I spent 20 years at the Carrier Clinic, which included seven years as director of research and four years as medical director. I started in the outpatient department and after a while I became director of education.

TB: So you started at the Carrier Clinic in the early 1970s?

AS: This was from 1972 until 1990. I started there with the lithium study. We put more manic patients into the study than any of the other participating centers, and some of those patients have stayed with me, so I've been seeing them every three months or six months for thirty years. We, also, occasionally, did drug studies, for instance, one with synthetic TRH in the treatment of depression. I never had the sort of results with TRH that Prange had. He had very good results, and he still thinks it works, but it didn't work for me. I sent him all the data on the study at his request. There wasn't anything there. I have been involved in other types of research including non-psychiatric drug research. I spent 20 years consulting for Squibb on phase I studies. So, what else can I tell you?

TB: What did you do after you retired from the Carrier Clinic?

AS: I've been teaching all along at the Robert Wood Johnson Medical School, first as associate professor, then in 1978, as a clinical professor. From 1990 to 1993, I went full-time with the medical school, as director of the addiction services. Then I retired, and since then, have been part-time in private practice, still doing some teaching of medical students.

TB: Are you still active in research?

AS: I'm still involved in drug studies, but this is just a very small part of my activities. Things have changed so much now. Max Fink wrote about it at length in your CINP series. I don't get much satisfaction from looking at a fragment of a study. In the old days, we wrote our own protocols, picked our own measures, saw all the patients, and wrote up the results. All of that is gone, we can't cry over spilt milk. There is not much we can do about it, so I don't get involved.

TB: When did you become a member of the ACNP?

AS: I must have become a member, about 1964, and became a fellow, in 1967.

TB: So, it was about 38 years ago. Have you served on any of the committees?

AS: No, I never volunteered for anything. Actually, George Simpson asked me to be on the ethics committee, and I did that, but I really didn't volunteer for anything.

TB: What do you think was your most important contribution to the field?

AS: It is difficult to point to one particular thing. Apart from drug studies, I was very involved in the brain wave studies with Leo Goldstein and was very impressed with his showing that schizophrenics have low variability in their brain waves. That seems to be pretty clear, although it hasn't really been followed up.

TB: Are you considering that one of your important contributions?

AS: I think that was important. I was very pleased with the various drug studies I did, but they are all obsolete now, and there have been a lot of other things that came along since. We did a nice four-year follow-up study with alcoholics, when I was at Carrier. That was the biggest study I did there. What we showed was that the treatment didn't work; no matter whether patients were treated there for a week, two weeks, or four weeks, the results were the same. One-third of the patients got better, one-third stayed the same, and one-third got worse. So, I think that was important, but for various reasons it wasn't followed up. What has happened since, is that because of insurance pressures, nobody is in the hospital for four weeks for alcoholism.

TB: As director of education, you trained probably a number of people. Is there anyone you would like to mention from those you trained or worked with during the years? You have already mentioned a few.

AS: We talked about Carl Pfeiffer, Leo Goldstein, and Henry Murphree, and I think I also mentioned Pete Penick. He died young, unfortunately. He was a very athletic man, kept very trim, but after a tennis game he collapsed with a heart attack; that was a great loss.

TB: Is there anything else we should cover? That we left out? What was your last publication? You seem to be still active in your practice, right?

AS: Yes.

TB: Well, let me ask you one final question. Is there anything you would like to see happen in the field?

AS: That's a great question—in the field of psychiatry?

TB: Psychopharmacology.

AS: Coming to this meeting over so many years, you can't but be impressed by the amount of fragmentation that is going on. In the early days of ECDEU, one could understand what all the different people were talking about. Now we have wonderful presentations with the latest cutting edge advances in imaging and genetics, and one wonders how much is accessible to people in unrelated fields. I mean, there may be 20 or 30 different fields in basic science being discussed, but very little overlap between them. In the old days, we sought out what was going on in related fields and could understand them. The knowledge has expanded so much that most of the work that goes on is beyond the comprehension of most of the people not directly involved with it. So, unfortunately, we're getting a Tower of Babel, where people don't understand each other's language.

TB: So you think that communication should be improved across the different areas in the field?

AS: Yes, but I don't know how; you're asking me what can be done, but I really can't think how, because it is so inevitable we become more and more fragmented.

TB: This is a reasonable note on which to end this interview. Thank you.

AS: Thank you.

62. DANIEL P. VAN KAMMEN

TB: This will be an interview with Dr. Daniel van Kammen⁶⁴ for the archives of the American College of Neuropsychopharmacology. It's December 10, 2001. We are in Hawaii at the annual meeting of the American College of Neuropsychopharmacology. I am Thomas Ban. So let's start from the very beginning: where and when were you born? If you could tell us something about your early interests, education, and how you got involved in neuropsychopharmacology?

DvK: I was born in Dordrecht in The Netherlands, in 1943. This meant there was still a year and a half to go before World War II ended. My parents were both physicians, and very early on, I got involved in research. My parents were very much interested in research; I was one of the first children to get tuberculosis inoculation with BCG after WWII and one of the first to get polio vaccination and those kinds of things. So there was always an interesting new development in medicine, as I grew up. Then, I went to the "gymnasium," which is a six-year program with science, such as physics, chemistry, biology, extensive math, languages, such as Dutch, English, German, French, Latin and Greek, and history and geography.

TB: Where did you go to the gymnasium?

DvK: In the town that I was born in, Dordrecht, 15 miles south of Rotterdam. Then, I went to the University of Utrecht and like my brother, my parents, and my grandfather, I was going to be a physician. During high school, I got interested in psychiatry. I was an avid reader from early adolescence, on Dutch history, world literature, poetry, and anything I could find in my parents' library. I was very much excited by that.

TB: So, you entered medical school because it was a family tradition and became interested in psychiatry while still in high school.

⁶⁴ Daniel P. van Kammen was born in Dordrecht, The Netherlands, in 1943. He received his M.D. degree at the University of Utrecht, in the Netherlands. He immigrated to the United States to begin his psychiatry residency in Johns Hopkins University School of Medicine, in Baltimore, Maryland. After residency, he did a fellowship at the Intramural Research Program of the National Institute of Mental Health in Bethesda, Maryland and then stayed on to do his own research. He then joined the faculty of the Department of Psychiatry at the University of Pittsburgh where he led a research program at the affiliated Veterans' Administration Hospital and eventually, transitioned to an administrative role. He left the VA to join the pharmaceutical industry with Johnson & Johnson. He was interviewed in Waikoloa Village, Hawaii, on December 10, 2001.

DvK: Right. Psychiatry was not a family tradition. We used to say, psychiatrists are reluctant physicians, but that seemed to be the obvious choice for me.

TB: During the period you were a medical student, pharmacological treatment was not very much accepted in psychiatry in your country. Is this correct?

DvK: In academia, there was still a strong influence of psychodynamics, and particularly psychoanalysis, but any experienced psychiatrist was very excited about the new developments in psychopharmacology. Rümke, who died shortly before I started to attend psychiatry lectures, was a great proponent of the emerging psychopharmacology. He was a psychoanalyst, but very interested in psychopharmacology.

TB: So, you did not know him.

DvK: No, but my brother, who is two years older, knew him.

TB: He was a very important figure in psychiatry. Wasn't he the one who first described the "praecox feeling"?

DvK: Indeed. He published a lot of good text books and case histories. He was known for the praecox feeling, which we don't rely on any longer for diagnosing schizophrenia.

TB: Did you have any contact with Herman van Praag?

DvK: Not at that time, but his book on *Psychopharmacology* had come out during the years I was a medical student. That was a tremendous help early on, before Donald Klein and John Davis wrote their book. Later, I did my Ph.D. thesis with Herman Van Praag and David De Wied, who was professor of Pharmacology in Utrecht. I was Herman's first Ph.D. after he became chairman of psychiatry. The title of my thesis was: "Studies with Amphetamine in Depression and Schizophrenia."

TB: Who succeeded Rümke?

DvK: Professor Plokker, who asked me, following my first year psychiatry exams, to become a junior resident at the Utrecht University hospital. That was very exciting; it was where I prescribed lithium to the first manic patient I treated, a 14 year old girl. I did my psychiatric clerkship at a State hospital, near Utrecht, and worked with a psychiatrist and a resident responsible for an admission unit of 30 beds and two chronic units of 60 to 70 patients. That gave me the opportunity to see psychopharmacology in action. As the psychiatrist, Dr Fuldauer, used to say, "These drugs

are supposed to work.” Many times, of course, we saw good results, but for chronic schizophrenia or bipolar patients, we needed better and different drugs.

TB: What year are we in?

DvK: Between 1966 and 1968. My clerkship was a two year program with the first year internal medicine, psychiatry, neurology, and the second year surgery, gynecology, obstetrics, and some minor programs, dermatology, ophthalmology, and ENT. Inbetween those two years, I did an interview tour in the United States. I started out visiting the Nathan Kline Institute, which wasn't called that as Nate was still alive. I visited several programs in New York City, including Bellevue, went through Boston to McLean Hospital and Mass General. McLean was the first program to offer me a residency position. I also visited the programs at Rockland State Hospital, Cornell, Rochester in New York State, Toronto, Pittsburgh, and UPENN before I went on to NIMH, where Lyman Wynne suggested I should talk to Joe Stephens at Johns Hopkins. I stayed in Bethesda at the house of Don Fredrickson, the Director of the Heart Lung Institute. What excited me in the United States was the emphasis on systematic clinical research. Out of that interview tour, I got about five offers and decided to go to Hopkins, because Johns Hopkins University was a great place for my fiancée to complete her Art History studies and finish her Ph.D. I also knew about Hopkins. I had spent some time at the American University in Beirut two years earlier, just before the six-day war in 1967, when Johns Hopkins was supporting the AUB Medical School and Hospital. Hopkins also offered a very eclectic program from psychoanalytic training to psychopharmacology. For all kinds of reasons, Baltimore suited me well. So, after I completed my medical training in Holland in 1969, I moved to the United States within two weeks of graduating and started the internship Hopkins had arranged for me. My psychiatric residency started in July 1970. Seymour Perlin was Residency Director and Gerald Frank was head of outpatient and psychotherapy. Joe Brady ran an experimental behavior therapy program; he was also very interested in psychopharmacology. Joseph Stevens was doing schizophrenia research. Sol Snyder, fresh from Axelrod's laboratory at NIMH, was my clinical supervisor in the second six months of my first psychiatry residency year.

TB: Was Joel Elkes the chairman of the department of psychiatry at Hopkins at the time?

DvK: He was there during my first two years and then left. Joel Elkes and Frank Ayd sponsored me later for the College.

TB: When did you get involved with the ACNP?

DvK: When I was at NIMH.

TB: How did you get to NIMH?

DvK: When I left Hopkins, I did a fellowship with Dennis Murphy, at NIMH. It was at that time I first attended an annual meeting of ACNP, in 1973 or 1974.

TB: Did you already have a career in psychopharmacology in mind?

DvK: When I was preparing a six month elective in my last residency year, I looked at all kinds of possibilities. Group therapy was very exciting in those days, and so was family therapy. I worked with Virginia Satir, the family therapist, where I had intensive training in family therapy that was delightful; it gave me insight into all kinds of clinical matters. I had the usual psychotherapy training, and I worked with Joe Brady in a study group on behavior therapy. So, I explored all kinds of interesting opportunities.

TB: Did you have any contact with Joel Elkes while you were a resident?

DvK: Joel was a visionary; he developed all kinds of educational programs. He was involved with Israel in developing mental health centers there; he was setting up the community mental health center in Columbia, Maryland, family therapy with Virginia Satir, and group therapy with Irvin Yalom, who had just left when I came. All those were started by Joel. Plus, of course, we had our psychopharmacology programs; Frank Ayd was there. Curt Richter, the diurnal rhythm scientist, had an office next to me, on the third floor of the Phipps Clinic. Joel would talk to us once a month, but not someone we had close contact with. If you wanted to talk to Joel, the story was you had to hide in the men's room, waiting for him.

TB: Did you do any research while a resident at Hopkins?

DvK: I did with Lino Covi and Renato Alarcon, a resident from Peru, who was working with Lino, on anti-anxiety and antidepressant drugs. Renato was my resident mentor. Every junior resident had an older resident as mentor. He is a great colleague and friend.

TB: What did you do after your residency?

DvK: I worked in Dennis Murphy's clinical unit and lab at NIMH.

TB: Did you have any interaction with Biff Bunney?

DvK: Not at the time, but later on. Originally I was going to be at NIMH only for six months, but Dennis offered me another year to finish our research. And during that year, Biff took over from

Lyman Wynn and created the Biological Psychiatry Branch that included Bob Post working in affective disorders, Elliot Gershon doing genetics, and Chris Gillin doing sleep studies. Judy Rapaport was there in child psychiatry, while Candace and Agu Pert with John Tallman were in the biochemistry laboratory. It was a great group of people. Then Biff asked me to set up biological and pharmacological research in schizophrenia.

TB: Could you say something about the research you did with Dennis Murphy?

DvK: I was studying platelet MAO activity and serotonin uptake in platelets in his lab and in the clinic, and I used the amphetamine challenge for predicting treatment response.

TB: So you used an amphetamine challenge to predict response to antidepressants?

DvK: Yes. It was a follow up of Jan Fawcett's first report.

TB: What did you find?

DvK: The higher they scored on the amphetamine response scale, the more they improved with the amphetamine challenge, the more likely they were to respond to antidepressants. It was really Dennis's idea to do that research.

TB: Was it regardless of the antidepressant?

DvK: The patients were mainly on imipramine or amitriptyline and that didn't seem to make a difference. We were also trying to block amphetamine induced hyperactivity in lithium treated depressed patients and were working on the effect of lithium on depression. Tom Insel later wrote up the effect of lithium in depressed patients. We also looked at urinary MHPG with Helmut Beckmann in Fred Goodwin's lab. Helmut became professor and chair in Würzburg, Germany and President of the CINP. To me, it was very exciting to have another European around because I still felt European.

TB: So your first clinical research project dealt with prediction of treatment response to antidepressants?

DvK: Right.

TB: And you had positive findings?

DvK: Right, Jan Fawcett had published on it first with Dennis Murphy. Predicting drug response has remained a very important issue.

TB: In spite of your positive findings, nobody is using the amphetamine challenge test. How do you feel about that?

DvK: It's disappointing; we had replicated Jan Fawcett's findings. But, in academia we are more interested in coming up with scientific data, rather than practical applications.

TB: Why was it dropped? It was not because it didn't work.

DvK: Most clinicians are uncomfortable using amphetamines if they don't have experience with it during their residency.

TB: When did you move from depression to schizophrenia research?

DvK: In the middle of 1974. That was an incredibly exciting time. We were talking about the role of dopamine in schizophrenia, but it was clear to me already that dopamine could not be the whole story. Not everybody got better by blocking their dopamine receptors. This was before it was demonstrated that neuroleptics block dopamine receptors.

TB: It was still a hypothesis.

DvK: We started to do lumbar punctures and endocrine studies in schizophrenia. Again I used amphetamine as a challenge test with the rationale that d-amphetamine enhanced dopamine effects. It was intriguing that the action of amphetamine was supposedly related to dopamine in schizophrenia, and to norepinephrine in depression.

TB: But in depression, it was a favorable response that predicted a positive treatment effect.

DvK: In schizophrenia we got an acute but short lived worsening in some, but not all patients.

TB: In what proportion of the patients?

DvK: About a third; I saw many flat and uncommunicative patients come alive after amphetamine.

TB: Did any of the mute patients start to talk?

DvK: Some mute patients improved briefly, but not all of them. According to the literature, some mute patient responded to barbiturates, some to LSD, and some to other substances. I reviewed the whole literature from the beginning of the 20th century on that topic. It starts around 1929, when the first observations with amphetamine in mute schizophrenic patients were published. In reality, the patient population with schizophrenia is very heterogeneous, insofar as amphetamine response is concerned. You see worsening, no change, and in others even improvement.

TB: Would you think those with worsening represent a different form of schizophrenia from those who don't change or improve?

DvK: We thought the nature of the response was state-dependent. If people were very psychotic, they were more likely to improve; if they just came out of the severe episode but were not stable

they were very likely to get worse. We had people who were very stable and who didn't change. So when we looked at patients' baseline, it predicted their response. We did not think chronic amphetamine treatment was a good idea but some people have used amphetamine to treat negative symptoms of schizophrenia. By the way, we tried naloxone and naltrexone in the Clinical Center. We were still looking primarily at dopamine, serotonin, and norepinephrine in schizophrenia, and I wrote a paper in those years entitled, "The Dopamine Hypothesis Revisited" because I thought dopamine hyperactivity did not fully explain everything in schizophrenia satisfactorily, even if dopamine activity seemed to move psychotic symptoms.

TB: Was that your first publication in that program?

DvK: That was probably the first paper from our schizophrenia program.

TB: Was it based primarily on your findings with amphetamines in schizophrenia?

DvK: It also included a review of the literature. The paper was not restricted to findings with amphetamine but included findings with L-DOPA.

TB: Did you find L-DOPA made schizophrenics worse?

DvK: I used L-DOPA only in depressed patients. But we used apomorphine, a dopamine agonist, and it did not have much of a behavioral effect in our hands. Burt Angrist, Michael Davidson, and Carol Tamminga used L-DOPA and found it made schizophrenia worse. I then developed a hypothesis about an interaction between GABA and dopamine in schizophrenia, and published it, in 1977. We followed that up with our first paper, in 1982, on GABA levels in the CSF. Our most important finding was the relationship of CSF GABA concentrations and negative symptoms. It was the first paper in which the idea that negative symptoms could be separated biochemically from positive symptoms in schizophrenia. Tim Crow had just started to separate his two syndromes clinically, at that time.

TB: Would you like to elaborate on the GABA-dopamine interaction in schizophrenia?

DvK: When Kim from South Korea reported, in 1977, that CSF glutamate was decreased in schizophrenia, it was dismissed by people. Now, we believe that glutamate affects dopamine and that causes psychosis, negative and cognitive symptoms. We presented data at the annual meeting of ACNP, which indicated that glutamate is the link between dopamine and psychosis.

We did a "path-analysis" to see which influences what, and in what order. Could it be glutamate, dopamine, then psychosis, and then negative symptoms? Or could the order be

dopamine, then glutamate, negative symptoms, and positive symptoms. The only model supported by the data was: dopamine → glutamate → psychosis → negative symptoms. I think we're going to see more data, which will shift interest from dopamine to glutamate and GABA, with possibilities for glutamatergic antipsychotics. I've always believed that even though dopamine is in all likelihood involved, where it is in the chain of events is not known. So, when we talk about an endogenous disorder, we don't talk about a β -endorphin or a norepinephrine or a GABA or a glutamate or a dopamine or a serotonin disorder, we talk about a multi-transmitter disorder. It probably means we need to move beyond the receptor, perhaps into the mitochondria, at one end, and to brain pathways, at the other. We're either dealing with second messengers or with completely different intercellular cascades that are altered, and probably not in one place, but in several. It's a whole different concept. We looked at serotonin, norepinephrine, peptides, the immune system, and membrane turnover. I got interested in the calcium channel binding protein, in 1980, because D₂ binding involves calcium binding. Calcium channel blockers seem to be more effective in bipolar mania. Or it could be a disconnectivity disorder; something that may involve impaired white matter. We need to rule that out because it's the most obvious one. Ninety percent of brain cells are white matter. So, if you study a disorder like schizophrenia, the world is still wide open.

TB: When did Tim Crow's Type 1 and Type 2 schizophrenia enter the scene?

DvK: Tim Crow published his first paper on the two types of schizophrenia, in 1979. Negative symptoms seem to be present before the major productive positive symptoms appear.

TB: When did Nancy Andreasen publish on her positive and negative symptoms?

DvK: That was, in 1981. She came up with a better scale than Crow. That was a very productive period; we started to look at CAT scans. Years earlier, during my residency, I treated an acutely psychotic patient who had a seizure. In those days we used to do skull x-rays and pneumoencephalograms; CAT scanning was not yet available. When the report on my patient's pneumoencephalography came back we saw the young woman had severe cortical atrophy and wide ventricles. I asked people, including Sol Snyder, what our findings meant, but nobody knew. Then, when the first CAT reports appeared, our findings made a lot of sense. Furthermore, there was an early paper by Professor Winkler, in the Netherlands, who had noted a similar finding in chronic schizophrenic patients with pneumoencephalograms, in the 1930's or 1940's.

TB: Were you able to fit all your findings together?

DvK: We never really were able to because we didn't have the statistical know-how at that time. But we did find a relationship between CSF GABA concentrations and negative symptoms. We also found that larger ventricle size was associated with lower HVA, DBH, and 5HIAA, as well as with more negative symptoms and worse premorbid functioning. We published a paper in the *Journal of Neuropsychopharmacology* where we reported that slow wave sleep, negative symptoms, and ventricle size were related. Interestingly, Krieg at the Max Planck Institute, followed that up in Huntington's disease, because there you also have negative symptoms, like apathy, decreased striatal size, and decreased slow wave sleep. But if you want to put all these numbers together, you really need to do statistical modeling in a larger sample. That couldn't be done at NIMH at that time. When I got to Pittsburgh, we started to use Bayesian statistics; we did statistical modeling with relapse prediction and random regression.

TB: When did you move to Pittsburgh?

DvK: In December 1982.

TB: So from the mid-1970s to the early 1980s you were at NIMH, in charge of research of the schizophrenia program, and in 1982, you moved to Pittsburgh. During those years at NIMH, surely you had fellows.

DvK: People like Sam Siris, John Docherty, Steve Marder, Paul Alexander, David Sternberg, J.C Garbutt, Carol Tamminga, Jack Rosenblatt, Gerry deFraities, Dan Hommer, Ken Malas, Dan Waters, Chuck Schultz, John Boronow, Phil Ninan, and several others were fellows on my unit. Jack Grebb was a fellow with me as a medical student.

TB: I suppose you have many publications from that period?

DvK: Over 150.

TB: Is there anything else you would like to talk about related to your research at NIMH?

DvK: We did a wide range of research. We showed that hemodialysis did not work in schizophrenia. The treatment trial was based on the assumption that endogenous toxins cause psychotic symptoms. Once we found that increased CSF MHPG and norepinephrine predicts an early drug free worsening, we gave amphetamine to patients on pimozide just before we switched them to placebo, and those that showed an acute increase in psychosis were the ones that worsened very quickly after the replacement of pimozide with placebo. There were two patients who got

better and remained asymptomatic for several weeks following pimozide withdrawal. This was all done with approval by the IRB at NIMH. When I went to Pittsburgh, we set up a research program that allowed us to study patients who were stabilized on haloperidol with cognitive tests, lumbar punctures, blood withdrawal, electrophysiological measures, polysomnography, CAT scans, and later MRI's. Then, haloperidol was replaced with placebo to see whether we could predict relapse. We found again that people who had elevated norepinephrine, even if they were somewhat stabilized, were the ones who relapsed quickly. In other words, you needed dopamine blockade to protect from the consequences of norepinephrine excess.

TB: Did you measure norepinephrine in blood and plasma as well?

DvK: In the CSF and plasma. So having elevated norepinephrine may actually be a destabilizing factor in the absence of D₂ blockade. We also found that patients with low DBH are more likely to respond to the dopamine blockade produced by antipsychotics.

TB: Is there any clinical indicator of low DBH?

DvK: We reported in our paper at NIH, published in *Science*, that good premorbid functioning was associated with low DBH.

TB: Was it followed up?

DvK: Joe Gelernter, who had worked with me in Pittsburgh as a resident, and then moved to Yale, followed up the low CSF DBH data.

TB: Was your research in Pittsburgh focused entirely on schizophrenia?

DvK: Yes, but I had become interested in post-traumatic stress disorder (PTSD) because I saw schizophrenia, also, as a potential disorder of stress regulation. In 1982, PTSD was a diagnosis that didn't exist. Particularly in the VA, there was a lot of controversy and people believed that PTSD starts out in the military as malingering. But I remembered from the post-World War II years, that people didn't talk about it that way. If you look at the literature, in the first five years following World War II, and also following World War I, there was an enormous amount of clinical descriptions of PTSD in the psychiatric literature.

TB: What about after Vietnam?

DvK: In the early 1980s, people started to realize the early negative reports on Vietnam veterans were not true. Then, with the DSM III-R, we got criteria for PTSD.

TB: What was your position in Pittsburgh?

DvK: I started out as full Professor of Psychiatry, and Chief of Psychiatry at the VA. That was the job I was recruited for. Within a few years, I became acting Chief of Staff, and then was appointed Chief of Staff at the VA. I also set up a laboratory and a clinical research unit for schizophrenia studies.

TB: Was Tom Detre the Department Chair?

DvK: Tom recruited me.

TB: I understood that you did electrophysiological studies and polysomnography in your research. Where did your experience, in these areas come from?

DvK: Chris Gillin taught me at NIMH. Chris and I did some sleep studies together in schizophrenic patients before and after amphetamine infusions in the pimozide study. Then, in Pittsburgh, I had a fellow from the University who was interested in sleep, Tom Neylan. He is now on the UCSF/Stanford faculty and the VA in San Francisco. Later Eric Nofzinger joined me and followed up on that work. Once we had the expertise, we published some very interesting data on the decreased level of slow wave sleep in drug free schizophrenia, and on the relationship between decreased slow wave sleep, wider ventricles and negative symptoms in schizophrenia. We started to look at the automated recordings and analyzed some of the spectral sleep data.

TB: Where did your support for research come from in Pittsburgh?

DvK: The research unit was fully funded by the VA. My research grants came from NIMH, VA, and from private foundations. When I started out in Pittsburgh, I had no experience with grant writing. At NIH, you wrote a four page proposal that was reviewed by the Institutional Review Board and then you went ahead. It was very simple and straightforward, different from writing a full-fledged 20 page scientific proposal for NIMH. I submitted two proposals from Pittsburgh to NIMH, one was on relapse prediction with norepinephrine measures and the other was treating psychotic patients with clonidine. I was asked by the NIMH site visit committee which one was more important for me? I was advised by the chair to go for both but when I said they're equally important, I didn't get funded. But in the next submission, we went for relapse prediction only, and I have been fully funded since, by NIMH, the VA, and private foundations.

TB: Could you tell us something about the clonidine studies you did?

DvK: We put patients who got worse after antipsychotic withdrawal on clonidine and placebo in a double blind fashion and we confirmed Bob Freedman's early findings with Dick Wyatt that clonidine has antipsychotic potential.

TB: What does clonidine do?

DvK: Clonidine is an α_2 agonist that acts mainly presynaptically.

TB: So you decreased, presumably, the norepinephrine in the synapse and by doing that you treated the hyper-noradrenergic condition?

DvK: That is correct. We also looked at cognitive changes with clonidine and showed improvement. Obviously, we did not get the most chronic patients because there is an issue with informed consent. We did informed consent in such a way that the patient had to tell us why they wanted to be in the program, what it was we were trying to accomplish, and what were the risks. We would not proceed if they could not answer those questions to our satisfaction. We believed from day one that a better-informed customer is more cooperative. For the same reason, we wanted families to be a part of that process. If the family didn't support it, the patient would most likely withdraw at an inopportune time. It is better not to waste anybody's time, including the patients, if it is unlikely they fully understand what you want them to do.

TB: You have collaborated with many people in your research.

DvK: I have collaborated with a lot of people in my career. Modern clinical research is a large collaborative effort, which requires a very diverse expertise, which nobody can bring by themselves to the table.

TB: Is there anything else you did in Pittsburgh we did not cover?

DvK: As I said before, I started out as Chief of Psychiatry at the VA, and in 1985, became Chief of Staff. At the same time, I was responsible for the clinical running of the hospital, so I became an administrator. Then, in 1994, we had healthcare reform and I became a member of the VA team mandated to re-invent the VA. That was very exciting. It was like having training in management on a level you very seldom get. At that time, the Hospital Director who I had worked with for years got another assignment and someone else came who had also been in the VA Healthcare Reform Group. She and I shared a clear vision about what we needed to do to implement the transformation of the delivery of care. That took a lot of time away from my research.

TB: So from the mid-1980s, you were moving more and more into administration. Were you able to continue with your research while you were busy with administration?

DvK: I was continuing with the sleep studies. Mary Kelly, who got her Ph.D. in Statistics in Pittsburgh, was my research assistant and I published with her on what happens to plasma MHPG and HVA when you discontinue haloperidol in schizophrenia. She moved later to Atlanta to become Faculty at Emory. Mark Beuger came to work with me as a Fellow from The Netherlands, and we wrote a paper about our CSF findings after haloperidol discontinuation. He became a psychiatric resident later. Allan Brown was a resident on the unit and later went to Columbia.

TB: What have you been doing since the mid-1990s?

DvK: I started to do studies for the pharmaceutical industry as a way of learning about new compounds.

TB: Could you tell us some of the drugs you worked with?

DvK: I worked with sertindole, olanzapine, quetiapine, risperidone, and ziprasidone.

TB: With mostly atypical agents?

DvK: Yes and a couple of compounds that didn't make it.

TB: Did you do any research with clozapine in Pittsburgh?

DvK: No, I did not. When Sandoz first came and talked to me about doing a study with clozapine, in the early 1980's, the unit wasn't ready and I didn't feel I could do a credible job. Later, I started to prepare for the Novartis Clozaril study on suicide prevention, just before I left for Industry.

TB: What happened to Sertindole?

DvK: Sertindole, because of a QTc problem, didn't make it in the US.

TB: Is there anything you would like to share with us about your experiences with the new atypical neuroleptics?

DvK: We found they produce fewer extrapyramidal side effects (EPS). Since then, issues like weight gain and Type 2 diabetes have emerged. The weight gain we see with these drugs in the community at large is a big problem. One thing that was very intriguing was their effect on negative symptoms. So, we looked further into negative symptoms because it seemed to me that some of the negative symptoms were secondary to EPS. Since then, that's been shown to be the case. We had a poster presentation in which we showed the gamut of negative symptoms in those who relapsed and those that didn't. In the early years, we saw people who got better for a while

after being taken off antipsychotics, which suggested some symptoms were secondary to antipsychotic use.

TB: Any other research you did in Pittsburgh you would like to talk about?

DvK: We have done a lot of work with membrane phospholipids and the immune system.

There seems to be a relationship between arachidonic acid turnover and cytokines and I'm sure we're going to see some more developments in those areas. TB: Why did you leave Pittsburgh?

DvK: During my last year in Pittsburgh, the VA decided to go ahead with a merger of two VA hospitals and I abolished my own position, assuming I would then spend full-time on my research. Then, I realized I was a general without an army. I also did not believe that writing 10 papers a year would make a dent in improving treatment options. Clinical development is hard to do in academia and I thought there must be other places I could do research. So, I started to look around and the only place I found where research could be done without spending all your time writing grants and building infrastructures was the Pharmaceutical Industry. The Research Institute of Johnson & Johnson hired me to develop topiramate (Topamax), an anticonvulsant for the treatment of bipolar disorder.

TB: Are you still with Johnson & Johnson?

DvK: Yes.

TB: And still in charge of the topiramate project?

DvK: Yes, but we also have positive data in alcoholism and bulimia.

TB: What is your title at the Institute?

DvK: I am the Global Medical Leader, which means basically the lead psychiatrist in developing the drug. So I deal with protocol design, overseeing execution of the trials, and safety.

TB: Could you say something about some of your ongoing studies with topiramate?

DvK: We are doing studies in mania. We use the Young Mania Rating scale (YMRS) as the primary end point. The basic protocol lasts three weeks, but the European regulatory agency wants 12 week data. It's intriguing because there's no precedent for doing 12 week mania trials and there is no way of statistically analyzing those trials because you lose 50 percent of your subjects even in those three week trials. When you're out at 12 week it's a big problem.

TB: So you're testing the drug in mania?

DvK: Yes. It also seems to work in depression and in prevention of relapse in bipolar disorder.

We see effects also in Gilles de la Tourette's.

TB: So it is working in the prevention of bipolar disease.

DvK: There are some intriguing case reports in treatment resistant depression but we don't know how good those are. Topiramate induces weight loss. It may work in eating disorders and a number of other indications as well, for example PTSD, treatment resistant OCD, etc. It is almost too good to be true. It has some cognitive side effects, though. TB: Are you doing your studies globally around the world?

DvK: Yes. We have clinical sites participating in South America, South Africa, Australia, Eastern and Western Europe.

TB: In what phase of development is the drug?

DvK: In Phase III. We hope by the end of next year, we'll go to the FDA; we'll keep our fingers crossed.

TB: Is there anything which we didn't talk about that you would like to add?

DvK: When I left Pittsburgh, I thought I had to resign my faculty appointment, but they said, well why don't you become an Emeritus? So, I'm an Emeritus Professor of Psychiatry at Pittsburgh University. I am also an adjunct Professor at the University of Pennsylvania and Columbia University.

TB: Are you involved with teaching?

DvK: Yes and no. What I do is grand rounds and I give talks when people ask me.

TB: Are you also seeing patients?

DvK: Not anymore.

TB: Anything else you would like to add?

DvK: Psychopharmacology has been very good to me and these are very exciting times. I am also involved these days in evaluation of new compounds.

TB: So, you are very interested in developing new drugs. There are tremendous unmet medical needs and our patients definitely need new effective and safe drugs. Have you been active in the ACNP?

DvK: I have been on the Membership Committee, the Committee on Government Industry Relations, and on the Protection of Animals Committee. The ACNP has always been my intellectual center. I hope to remain active.

TB: Have you written or edited any books?

DvK: I have not written any book, I've edited a book series on *Research and Clinical Developments in Mental Health*, and a book with Malcolm Weller about *Mental Health*.

TB: You are still very active and you seem to intend to stay active.

DvK: I am very grateful for the opportunities I have had and still have, and particularly for the wonderful people I have worked with.

TB: So on this note we conclude this interview with Dr. van Kammen and I would like to thank you for sharing this information with us.

DvK: Thank you, Thomas.

63. MYRNA M. WEISSMAN

TB: This will be an interview with Dr. Myrna Weissman⁶⁵ for the Archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the college in Waikoloa, Hawaii. It is December 12, 2001. I am Thomas Ban. Could you tell us where you were born, brought up, your early interests, education, and so on?

MW: I was born in Boston, Massachusetts and was an only child. My father had a small business and my mother stayed home. I went to Brandeis University and graduated when I was about twenty. The fields women were shunted into were nursing, social work, or teaching. I did social work, got married, and had four children. I didn't like social work.

TB: Where are we timewise?

MW: In the late 1960's.

TB: Late 1960's.

MW: Right. In 1970, I entered graduate school at Yale for a Ph.D. My four children were age six and under, I was thirty, and decided I had to do something with the rest of my life. Fortunately, that was the beginning of the women's movement, because otherwise, they wouldn't have let me into graduate school, especially at Yale. My first plan had been to develop real estate. We lived in Bethesda, Maryland, my husband was a scientist at NIH, and real estate in the area was rapidly developing. I saw an opportunity to do something creative that was also very lucrative. So, I took out my real estate license but then my husband accepted a job at Yale.

We arrived in New Haven and I realized it was not a place for real estate development, so I'd better find something else. I got the most interesting job of my life with Gerry Klerman, working two days a week on a study of the maintenance treatment of depression to prevent relapse and recurrence. I was the social worker with no experience and small children who didn't want to work more than two days a week or an academic career. I wanted something fun and this seemed like an important project. I was hired to help get started until they found an experienced full-time

⁶⁵ Myrna M. Weissman was born in Boston, Massachusetts, in 1940. After working as a social worker, she entered graduate school at Yale University in New Haven, Connecticut for her Ph.D. degree, and then, joined the faculty of the Department of Psychiatry and Epidemiology of the Yale University School of Medicine. Subsequently, she became a member of the faculty of the Departments of Psychiatry and Epidemiology in the College of Physicians and Surgeons and the School of Public Health at Columbia University in New York City, New York. She was interviewed in Waikoloa, Hawaii, in December 12, 2001.

social worker to run the project, travel, and do psychotherapy. It was difficult to work with young children. My first day of work, the baby sitter didn't show up. I remember Gerry saying, "Well, bring them along." My 18-month old and I arrived and the meeting was about life events. Gene Paykel was there with Gerry gearing up for the maintenance study and they had just obtained their first data on life events. It showed more life events in six months prior to onset of depression compared to controls in the same time period. Life event exits seemed more important than entrances.

TB: You had your degree in social work but no prior experience?

MW: I was quite inexperienced but I knew this was an important study. It was interesting and I didn't want to spend my time doing something boring.

TB: So you found the people stimulating?

MW: Oh, they were so interesting. There were no guidelines on what to do and they had a hard time finding this super social worker to run the project. Gerry didn't like to waste time and gave me Aaron Beck's hand written manual on cognitive therapy, about a hundred pages long. He told me to design the psychotherapy component and specify the procedures for the depressed patients, mostly women. I was the perfect person to do that because I had no pre-existing ideologies. I started reading. I read Bowlby & Rutter, the life events literature, and Parsons and Bales, working very closely with Gerry. I suggested we should define the dose of the psychotherapy like a drug, then the duration, quality, and who does it. That was easy. Then we started to get into the tough part. What's important in depression with depressed middle-aged women who have children? I knew something about children. I remember saying, these patients should know they have depression; it shouldn't be a mystery. So, we began by going through a diagnostic procedure with the patient explaining what depression is, its symptoms and its course. Then we needed to figure out how it started. We developed the idea of an interpersonal inventory enquiring what was going on, and who the important people in the patient's life were. While depression is a biological disorder, what's happening in life, probably triggers it. We developed a draft manual and Gerry used to say, "You have to be specific, you can't just say, be supportive. You have to specify what you do to be supportive, write scripts." I was working two days a week, but most of this was done on the other days at home. I only had the obligation to go in to work two days a week, which freed me up.

TB: So, you did some of your work at home?

MW: I did most of it at home. Finally, we had a manual, maybe 50 pages. Then Gerry said to me and to Gene Paykel, “Now you have to define the outcome. Social function should be the outcome of psychotherapy. We expect that drugs will help symptoms, make people sleep better and eat better, feel less hopeless, but psychotherapy will have effects on how people function, so define the social functioning.” I remember going home with a stack of papers, all the articles I could find on social functioning. After that, at Gerry’s request, I wrote a review for the FDA on Social Functioning Scales, which was one of my first publications.

TB: When was that?

MW: It was in the early seventies. Gerry had left for Harvard but he called and said, “The FDA needs a review of social adjustment scales, could you do it, and make it like a consumer report?” I did, and we published it in *Archives*. As a review, it was quoted a lot. The scales fell into two categories: Those designed for studies of schizophrenia, where functioning was assessed at a low level. For example, do you brush your teeth and take your own bath? Our patients were depressed women, living at home taking care of families, so these scales were not appropriate. The other scales were for college students and assessed dating. Again, our patients were married and had children. Barry Gurland had a scale that he’d been working on for years that had many items appropriate for us, but it didn’t cover children and extended family, so, working with him, we developed the Social Adjustment Scale. Now, that we had the scale and a manual, we were ready to begin the study but Gerry pointed out we had to validate the scale. Not having studied psychometrics, I wasn’t sure what was needed. With the help of Jerry Myers in New Haven, who worked with Hollingshead and Redlich, we identified an appropriate normal sample. This led to a book, *The Depressed Woman, a Study of Social Relationships*, published in 1974, by the University of Chicago Press. After Gerry left for Harvard and Gene returned to England, I went to graduate school. I completed graduate school very quickly because Brig Prusoff and I were running the remaining studies left at Yale. Gerry was the Principal Investigator and subcontracted the studies to us.

TB: So your book was published before your graduation?

MW: It came out in 1974, the year I got my degree.

TB: Did you use it for your dissertation?

MW: No, they wouldn't let me because the writing began before I started graduate school.

TB: What did you do for your dissertation?

MW: My dissertation was much less interesting than the book. It was the follow-up of the maintenance study.

TB: Could you use the data from that study for your dissertation?

MW: I could, because I had been heavily involved in the study. I designed the psychotherapy and the major outcome measure and had been involved in data collection and supervising the staff. I didn't do it alone and could never have done it without Gerry, Gene Paykel and Brig Prusoff.

TB: Could you tell us something about the results?

MW: One hundred and fifty depressed women received either drugs or high contact psychotherapy with placebo or no pill. First, they received an open trial of amitriptyline. If they responded, they were then randomized into the six cell factorial design. The major finding was that amitriptyline, over eight months, prevented relapse compared to placebo or no pill. Psychotherapy had no effect on preventing relapse but had an effect on social functioning. Since patients had problems in both areas, those who had both medication and psychotherapy had the best outcome. This was the first evidence for the efficacy of combined treatment. Gerry and Gene were very dubious about the efficacy of psychotherapy. No one had ever shown a psychotherapy effect so they were surprised to find one.

TB: Were you also involved in the "life events" studies?

MW: No. That was Gene and Gerry's work.

TB: I see.

MW: My one involvement in life events came from a graduate school course. I was learning new statistical approaches and concepts in a class on relative and attributable risks. I suggested to Gene this might be useful in presenting life events data. So, he did that and published a paper which showed that attributable-risks were much higher for depression than other disorders. So, we collaborated closely, even from afar.

TB: And, then, Gerry and Gene left?

MW: Right. When Gerry and then Gene left Yale, I finished the follow up of the maintenance study. Then we wrote another grant on acute treatment with drugs and interpersonal therapy. Mason DeLaverne was hired as the treating physician. He was a semi-retired internist, a very nice

man, who took care of the patients. One morning, I arrived to find a waiting room full of patients and no Mason.

I called his wife and learned he'd had a heart attack and stroke and died that night on the stage, while performing on the violin. So there we were Brig and I, no doctorate degree between us, and patients. That was trial by fire. We hired another doctor and just continued. We were off campus at a little house on Park Street, so we didn't cost the University anything. In fact, we brought in money from overhead on the grants, so nobody paid much attention to us. We did what we wanted and had a great deal of fun.

TB: When did you finish your dissertation?

MW: I finished up my dissertation, in 1974. Then we wrote a collaborative grant with Gerry as the principal investigator at Harvard, while I was the principal investigator at Yale; now I had my Ph.D. This was an acute treatment study, because we argued that psychotherapy would have more of an effect from the beginning, not just after patients responded to medication. It was much easier to do a 16-week acute treatment trial, using amitriptyline and what we had now named high contact, Interpersonal Psychotherapy (IPT). Bruce Rounsiville and Eve Chevron began to work with us and we put together a comprehensive manual, which was published, in 1984. Gerry and I did not want to train people in IPT, when it had never been used outside of Yale and Harvard. We wanted to wait until there was more evidence for efficacy.

TB: Did you work full time by then?

MW: After I got my degree, in 1974, I went full time.

TB: I suppose by then the children were in school all day?

MW: They were still young, but I worked at home a lot, so I never worked nine till five. I would go to work very early after the children went to school and I was always back when they got home. I would work in the evenings and on weekends, but we were a working family. We all worked. If I had any major writing to do, I would stay home. I was very close to home, so if I wanted to go to the children's performance or help at the school, I did. I had no bosses.

TB: Did you have your own projects?

MW: I had several grants, because it wasn't difficult to get funded if you had ideas. I was also involved in research with Herb Kleber at the Drug Abuse Unit. We were outside the main stream in psychiatry, the Department was very psychoanalytic. Herb was next door in the same complex,

a couple of blocks from the medical school. He had a big government contract to study methadone for heroin addicts, and invited Brig and I to do the part on depression. Brig and I had a weekend to get the project written. I knew nothing about methadone but Brig's husband was a very prominent pharmacologist, so we decided she should take the methadone part and I would write the depression part. We wrote that portion of the grant on the effects of methadone on mood using the assessments from our clinical trial. We only needed an additional section on the pharmacology of methadone and its effect on mood. The grant was funded, and suddenly, I was studying drug abuse. There were two other grants that came soon after. One was a very large grant to study co-morbidity in drug addicts and the other was to do psychotherapy, IPT, added to a standard program for drug addicts to see if it improved the outcome of methadone treatment.

This was in collaboration with Bruce Rounsaville at Yale. ITP didn't have an effect and it was also negative in another sample of drug addicts. That, to us, was reassuring. If you have something that works for everything, you probably don't have anything.

TB: Were you on the faculty by that time?

MW: I was an Assistant Professor and I had the maintenance study follow up, the acute treatment study, the methadone depression study, the co-morbidity study, and psychotherapy opiate studies. It was a big operation.

TB: You moved ahead fast on the academic ladder.

MW: I got promoted to Associate Professor and I can't remember when I was made full Professor, but I was the first woman to get tenure in the Department of Psychiatry at Yale, and I was a Ph.D. Interest in research became salient and Boris Astrachan, head of Community Mental Health, was a supporter and really pushed for my tenure.

TB: Is your Ph.D. in Epidemiology?

MW: It's in Chronic Disease Epidemiology.

TB: You had joint appointments in psychiatry and epidemiology?

MW: Yes.

TB: How long did you stay at Yale?

MW: Well, I stayed with Yale until 1987.

TB: 1987?

MW: Yes, a long time. I liked Yale. I was very happy there, but by that time, Gerry and I were married, living in different cities and I did not like that. My career was not as important as having a real life and my children were older. I was going to move to Boston, but there was no tenure job with Harvard. I was afraid to move to a non-tenured position. Gerry was willing to move to Yale, but they didn't have anything for him. Then, we got these great job offers in New York.

TB: So, you moved to New York?

MW: Gerry moved to New York, in 1985, and I moved, in 1987. Gerry was working at Cornell and it was easy, because he worked a couple of days in Westchester and we lived in Woodbridge, a forty-minute trip. We wanted to be in the same city, so we moved.

TB: Did you work together or did you have your own projects?

MW: We worked together, but also had different projects. When I was at Yale, in the 1980s, we had the Epidemiologic Catchment Area (ECA) study. We obtained the first rates for psychiatric disorders in the community, using modern diagnostic criteria. That was like a dream for someone who was an epidemiologist. Jerry Myers, who was a sociologist, had done major work on community surveys, using the older techniques measuring symptoms, not diagnoses. Together, we wrote the first application to do the ECA and got the first grant. That was followed later by sites in St. Louis, Baltimore, North Carolina, and California.

TB: Could you tell us about the study?

MW: The ECA surveyed eighteen thousand people in five US communities, using the Diagnostic Interview Schedule, which became DSM-III. It was developed by Lee Robins, Ph.D. and could be used by lay interviewers, because it was highly structured but generated the diagnoses used in clinical psychiatry. In the New Haven site, we surveyed eight thousand people with an over sample of the elderly and Black Americans. North Carolina had a rural sample. People developed their careers from that study. Marty Bruce, who is here at the ACNP, was my post-doc, and she got interested in geriatric psychiatry. She took over a follow-up sample and wrote her own grant. So, there was a lot going on. We still had funding from the ECA. Gerry wasn't involved in that. But while Gerry and I sometimes did separate studies, he had some on HIV we always talked with each other about what we were doing.

TB: What did you find in the ECA?

MW: In the ECA, we found that the rates of depression were fairly high, the rates of schizophrenia were what we had expected, about one percent, and so were the bipolar rates. Sex differences in depression were what we expected; about two to three fold greater in women than men. The major surprise was that most of these disorders begin in the young. We thought of depression, bipolar, and the anxiety disorders as conditions of middle aged people. What we found, consistently, across all the sites, was that these disorders begin often in adolescence, and certainly, by young adulthood. That didn't mean that older people didn't get depressed, but these were usually recurrences. So, the biggest contribution of the ECA was turning the focus on young people and their high rates of psychiatric disorders. There have been similar findings in subsequent studies like the National Comorbidity Survey (NCS). I then got interested in Genetic Epidemiology and started to do family studies of depression and panic disorder. These continue and I still am studying the grandchildren of our sample from New Haven. Now we are doing Magnetic Resonance Imaging (MRI) studies of three generations, at high and low risk for major depression (MDD). We presented the first findings from the three generations study at this meeting.

TB: What did you find?

MW: We found that the children of depressed parents have very high rates of depression; as compared to children of controls and that these depressions begin early, continue, and recur. The relative risk is about a three or four fold increase. We have followed them to adulthood and now find that the grandchildren carry the same risk. The sequence that we saw in the grandparents, the parents, the second generation, and other grandchildren is that they begin with pre-pubertal anxiety disorders. Around adolescence, you see the emergence of depression, and for some, in adulthood, substance abuse, especially for males. The risk is carried to the grandchildren of whom we have data on the first one hundred and thirty individuals. It's a first look, it's not clean data, but you can see there is over a fourfold increased risk in the grandchildren, based on their grandparents' depression status. That's a sturdy finding and others have found the same. The grandchildren are all in New England. We still have a team at Yale and have added neuropsychological measures, EEG, startle response, and now MRI and genetic studies.

TB: How did you measure the startle response?

MW: This is work done by Christian Grillon, who was at Yale and is now at NIMH. They use a puff of air and measure the startle response. There's work in animals to show which neural circuits

might be involved in anxiety, as reflected by the startle response. Brad Peterson is now at Columbia and is an excellent neuroimager, who was at Yale, and still has a team there. The next phase will be neuroimaging in these children and their parents and grandparents. That doesn't mean the environment isn't important, but we know that these children are carrying a risk that is stable and sturdy across the generations. That work continues and we are now collecting blood for DNA.

TB: What would you consider your single most important contribution?

MW: I don't know.

TB: You did several studies which had an impact on the field.

MW: A lot of the things were done that are now standard. So, no one is going to say, "She did it." That's good, because it means it's been incorporated. I feel that I helped bring epidemiology to psychiatry. I think IPT is a contribution. There are now numerous clinical trials and adaptations with an international society of IPT. We have a book on that, which came out, in 2000 and another in 2007. The Social Adjustment Scale has been translated into numerous languages. The high risk studies showing the transmission of depression across generations is a finding of major importance.

TB: You mentioned that you brought in psychiatric epidemiology. Is there anyone else who had been involved about the same time doing the same kind of research?

MW: Lee Robins, of course. She was over a decade ahead of me and did those wonderful studies of disturbed children growing up. I modeled my thinking about depressed children growing up on her work. It was Lee with Bob Spitzer who developed the Diagnostic Interview Scale (DIS), which made the first epidemiologic studies in the community possible. She has made major contributions so I would say that she was there before I was.

TB: So she was there before you?

MW: Yes.

TB: Anyone else you would like to mention?

MW: In epidemiology?

TB: In epidemiology.

MW: Bob Spitzer is a psychiatrist, but his work standardizing DSM diagnoses made epidemiology of psychiatric disorders in the community possible. There's a whole new generation. Ron Kessler is a leader in psychiatric epidemiology. His work began in the 1990's and he's doing major work

on cross national epidemiologic studies with the World Health Organization (WHO). He has an industry going and has done incredibly good work. I would consider him a leading person in psychiatric epidemiology. Adrian Angold, Jane Costello and Peter Lewinsohn have done epidemiologic studies in children.

TB: Your research was not been restricted to epidemiology but extended to genetics, biologic measures, and treatments. Is that right?

MW: We have a field that is much more developed and is now making the translation to biology. I don't want to keep doing the same thing. I could do another four high risk studies and show that the children of depressed, anxious, or alcoholic parents have different patterns, but it wouldn't be very interesting. Having laid the groundwork, the next step requires a serious collaboration with people in biology. In this phase of my research, I am working in close collaborations with other investigators. I have a genetic linkage study in panic disorder; a sibpair genetic study in depression, and a study of fear and anxiety where I work with molecular biologists. I'm not a molecular biologist and never will be. I don't even understand it at a deep level, because I don't have that background, but we work very closely together. I lead the collection of the families, the design, and the definition of phenotypes. I collaborate with Brad Peterson and others at Columbia on neuroimaging. I am very happy to have the people I collaborate with write the papers and lead that part of the research.

TB: Can we get back to the IPT? What is its current status?

MW: It's been adapted for many conditions and used in a recent study on bipolar disorder. There's much more enthusiasm about it in Europe, Canada, Germany, Australia, and New Zealand, where it's required in some training programs. Our study of depressed patients in Uganda using IPT is one I am the most proud of.

TB: It was a treatment developed by Gerry and you, right?

MW: Gerry was the major thinker in IPT. It came from his simple notion that despite the obvious biological basis of depression, the episodes are triggered by events, usually interpersonal. This notion is now supported by genetic studies done by Caspi.

TB: I see.

MW: What people are asking now is: what are the components of IPT that might be combined with other treatments? I don't have a problem with that. There is great satisfaction in doing something well and seeing it endure. It feels very good.

TB: Opening up a new field?

MW: Opening up a field.

TB: What are you working on now?

MW: What I try to do is things that are interesting to me that I can believe in. To do the same thing is easy, but not interesting, I'd rather go shopping. There's a lot of mechanics in research that are not pleasant, getting through Institutional Review Boards (IRB), writing grants, dealing with the administrative issues. It can be tedious. But, if you're not doing it in the service of something that's interesting, or that might provide an answer, it's not worth it. So, I've tried to keep in the areas that I believe will lead to answers. The most interesting study we're working on now has to do with answering a question that comes from the high-risk studies. We have shown that the children and the grandchildren of the depressed parents and grandparents don't have a very good prognosis. On average they don't do well. It's incumbent on us to do something clinically to figure out how you would intervene. We don't know very much about the treatment of children but we know a lot about the treatment of depressed adults. What if you vigorously treated a depressed mother? Could you have an impact on forestalling or preventing the illness in a child? We completed this study and remission of the mother's depression resulted in significant improvement in her children's symptoms. This was published in *JAMA* in 2006 and attracted considerable attention.

TB: Your work is widely known. Are there any awards you received you would like to mention?

MW: Awards are only important if you don't get them. I was very pleased to get into the Institute of Medicine. In May 2007, I am getting an award from the Society of Biological Psychiatry. That really pleases me as I am not a biologist.

TB: Didn't you get the prestigious Anna Monika award?

MW: Yes, but that was really Gerry's.

TB: When did you get involved with the ACNP?

MW: When the maintenance study results came out and we presented them at the meeting. People were really interested.

TB: Have you served on any of the committees?

MW: I have been on many different committees and on Council. I rarely miss an ACNP meeting. It's like family.

TB: Is there anything else you would to add, personal or non-personal?

MW: Well, my biggest loss was Gerry. He died April 3, 1992.

TB: But, you seem to be keeping very active?

MW: Yeah, I'm very active and I have great children. I have a son, who is a successful scientist. He has a Howard Hughes Unit at UCSF and is a structural biologist. I remarried last year to Marshall Nirenberg, a great man who won the Nobel Prize for deciphering the genetic code. I have three wonderful daughters, one who left law to become a psychiatric epidemiologist.

TB: So she follows you?

MW: Only a little. She is her own person. And, I have another daughter who is also an epidemiologist and a physician. She's in infectious disease at Yale, running AIDS programs. And, I have another daughter, who has an MBA, taking a business route and is running a big medical practice.

TB: So all of them seem to be following in your footsteps?

MW: Yes, in that they all have careers that they enjoy. I also have seven grandchildren.

TB: You have seven grandchildren? That's great.

MW: Yes.

TB: Well, I think I would like to thank you for sharing all this information with us.

MW: Thanks for asking me.

TB: Thank you.

MW: It's an honor.

64. PAUL H. WENDER

TB: This is an interview with Dr. Paul Wender⁶⁶ for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. We are at the annual meeting of the College in San Juan, Puerto Rico. It is December 11, 2002. Could you start, Paul, from the very beginning?

PW: I was born, in 1934, in Manhattan, the offspring of a psychiatrist who was psychoanalytically trained by one of Freud's disciples and a mother who was a social worker. One result was that I become interested in psychiatry from an early age. I went to private school and then to Harvard College, where I majored in biochemistry, but became quite interested in behaviorism and learning theory because these were relatively hard psychological sciences. I'd asked my father when I was a freshman to let me read something of Freud's to get a feeling for psychoanalysis, and he sent me a copy of a General Introduction to Psychoanalysis. I peppered the margins with "how does he know this," "what evidence does he have for making this statement," and came to question Freud's provocative, but unsubstantiated statements. I went to Columbia Medical School, where I did my physiology thesis on a certain aspect of Pavlov's work and, following an internship in medicine at Washington University, I began training in psychiatry at the Massachusetts Mental Health Center, in 1960. It was totally psychoanalytic. I found myself in the position of the little boy in the fairy tale of the emperor's new clothes. None of these people had scientific clothes on. I found it entirely impossible to comprehend schizophrenia on the basis of psychodynamic theory. I read the descriptive literature, the German literature on twins and on family studies, and became convinced that schizophrenia was a genetic disorder. I realized that neither family studies nor twin studies would prove the role of genetic factors because individuals who developed schizophrenia usually grew up under the psychological influence of schizophrenic parents. So, the effects of heredity and environment were confounded. I was so dissatisfied with the teaching and non-

⁶⁶ Paul H. Wender was born in New York, New York, in 1934. He received the M.D. degree from Columbia University College of Physicians and Surgeons. Following an internship in medicine at Washington University, in St. Louis, he completed a residency in psychiatry at the Massachusetts Mental Health Center in Boston, Massachusetts. He was drafted into the Public Health Service and became a fellow at the Intramural Research Program of the National Institute of Mental Health in Bethesda, Maryland. He, subsequently, completed a fellowship in child psychiatry at Johns Hopkins University in Baltimore, Maryland. He, then, became a member of the faculty of the University of Utah School of Medicine, where he remained until his semi-retirement during which he was a consultant at Harvard Medical School at McLean Hospital, in Belmont, Massachusetts. He was interviewed in San Juan, Puerto Rico on December 11, 2002.

teaching I received during my residency that I and a number of other residents organized a seminar on schizophrenia, in which we presented papers. The most prestigious member to be of our group was Eric Kandel, who was at that time a fellow psychiatric resident; many of the group later went into research. I wrote my paper on the origins of the concept of dementia praecox, taking advantage of the fine medical libraries in Boston. In 1962, I was drafted into the army and by a great fluke of luck managed to go to the National Institute of Mental Health and avoid doing psychiatric service in Korea. There I did some work with Bob Feinberg who was studying sleep and dreaming in schizophrenia and also did some research on the relationship of early social behavior in children and their later cognitive functioning. I submitted my seminar paper to the editor of the *American Journal of Psychiatry*, a man who had been trained by Kraepelin, and he accepted the paper and requested that I make one addition to the paper; a quote from Kraepelin. It was Kraepelin's modest statement, "We are always standing at the beginning." TB: When was the paper published?

PW: The paper, my first, was published in 1963, and that was a delight to me, my mother, and my father. About 1963, I was still reading extensively about schizophrenia, and I hit upon the idea of using adoption to separate the effects of nature and nurture in the etiology of the disorder. The beautiful thing about studying adoption is that the people who supply the genes and the people who supply the environment are two separate groups. My first approach was to study the adoptive parents of patients with schizophrenia at Johns Hopkins. To continue the study, I needed more money, so I went to the head of Intramural Research at NIMH, Bob Cohen, told him what my research needs were and how the research might be expanded. He told me that within the past several weeks two senior investigators had come independently to him to request money for adoption studies. One was Dr. David Rosenthal, chief of the Laboratory of Psychology, and the other was Dr. Seymour Kety, chief of the Laboratory of Clinical Science. Bob Cohen suggested I talk to them, and I did. I was not sure whether they would want me to collaborate with them. They had discussed their idea with Bob earlier than I did but they welcomed me as a full collaborator. This led to the Danish adoption studies of psychiatric disorders. One of the things that I wanted to do was to study individuals born to schizophrenics and adopted by normal parents. But it was very difficult to acquire such a sample. At that juncture, a visiting psychologist came to the NIMH and told us about his research in Denmark and about the existence of superb registers which would

enable us to do this kind of study. He put us in touch with the Danish psychiatrists, with whom we then collaborated, Drs. Fini Schulsinger; Joseph Welmer; and Bjorn Jacobsen. We initiated two studies. In the first study, in which Seymour Kety was the principle investigator, we wanted to investigate the biological and adoptive relatives of adopted schizophrenics and as a comparison group, the biological and adoptive relatives of adopted normal subjects. The issue was how to find them? The Danish registers contain information about all child adoptions by non-family members; in Copenhagen there were 5500 and we decided to examine all those who were between the ages of 18 and 45 and who had been placed in adoptive homes at an early age. The question was how to find which of them had schizophrenia? This was easy to determine because there was another register; the Institute of Human Genetics which listed the names and diagnoses of all Danes admitted to psychiatric hospitals. We determined that 600 of the adoptees had a psychiatric hospitalization, of which 33 were diagnosed as schizophrenic. As a comparison group we chose age and sex matched adoptees who had never received a psychiatric hospitalization. The names of the biological and adoptive parents of the schizophrenic patients and controls were given in the adoption register. The next question was how to locate them. Once more a register came to our aid. Every time people move in Denmark, they must register with the police, report their address change, and state the names of all people with whom they live. This enabled us to find the names of what other children had been born to the biological parents of the schizophrenic adoptees. Similarly, we were able to locate the adoptive parents and siblings of the adopted schizophrenics. We had the participation of a very vigorous young Danish psychiatrist, Bjorn Jacobsen. He had marched all over the peninsula, Zealand, where Copenhagen is located, and Jutland, which protrudes from Germany to interview all the adoptees and their relatives. One of the things I had also become very interested in was what was then called borderline schizophrenia, or “schizoidia.”

TB: Schizoidia?

PW: This was not a recognized diagnosis in DSM II, but it was a pet love of mine, and I had designed a structured interview for diagnosis which examined signs and symptoms of “borderline” schizophrenia. Hospitalization records and interviews, when possible, were obtained from all the relatives, biological and adoptive, and blind diagnoses were made by Drs. Kety, Rosenthal, Schulsinger, and me. The most exciting day I ever experienced in science was the day after Drs.

Kety, Rosenthal, and I had diagnosed all the relatives blindly. With our Danish collaborator, Dr. Fini Schulsinger, we opened the envelopes which had been sealed by research assistants. Lo and behold, we found the genetic hypothesis substantiated; there was an increased frequency of schizophrenia and schizophrenia-like disorders only among the biological relatives of the adopted schizophrenics. This proved two things. First, there was a genetic contribution to schizophrenia. The early family studies and the twin studies had been correct. Second, and this was of great interest to me, schizophrenia occurred along a phenomenological continuum, which we referred to as a schizophrenic spectrum. The individuals we called “borderline schizophrenics” were included in DSM-III and designated as “schizotypal personality disorder.” That was a major contribution, because the word “spectrum” became widely used in the description of many psychiatric disorders. There is an OCD spectrum, an autistic spectrum, and a depressive spectrum. So the idea caught on.

TB: What about the second study?

PW: The second major study used a different strategy to evaluate the psychiatric status of four groups. First we examined the adopted away individuals who had a biological parent who was schizophrenic, second, people born of normal parents who were adopted, third, the most unfortunate group, people who had the good fortune to be born to normal parents but the misfortune to be adopted by schizophrenics, and fourth, people born to and raised by schizophrenics. The interviews of all these subjects were performed by Dr. Joseph Welner. What we found substantiated the other study; compared to the biological offspring of normals the adopted away offspring of schizophrenics were at increased risk of schizophrenia and “schizotypal personality disorder.” The way DSM-IV constructed this diagnosis was by studying all the people who we had designated as borderline schizophrenia and extracting our clinical descriptions. Another finding was that being adopted away from a schizophrenic parent did not attenuate the disorder. These subjects did just as badly as if they were raised by their biological parent. That is not to say that these unfortunate individuals may not have had a more difficult experience, having a biological parent who was schizophrenic, but it did not increase their risk of schizophrenia. The last comparison group consisted of people born to normals and adopted by schizophrenics. There was no increase in schizophrenia, but they told the interviewing psychiatrist that they had very unusual and peculiar adoptive parents. To study so called “schizophrenogenic” parents we did a

study in the States where I interviewed the adoptive parents of schizophrenics compared with the biological parents of schizophrenics and a comparison group of normal subjects. Here we found that the adoptive parents were more psychologically disturbed than the parents of normals; they were depressed and anxious. They had one child, they were now 65 to 70 years old, and they were concerned about what would happen to their chronic schizophrenic child when they died. To control for the effects of parents on the child, we replicated this study with one change. We studied the adoptive parents of schizophrenics and the biological parents of schizophrenics, and the biological parents of nongenetic patients with mental retardation. The parents of the mentally retarded children were in the same position as the adoptive parents of schizophrenic children. They were 65 or 70, had a seriously impaired child whom they had been caring for an entire lifetime, and they were terribly concerned about what would happen when they died. The adoptive parents of schizophrenic children were no more anxious and depressed than the parents of retarded children. The psychological difficulties in both groups could be seen as the effects of rearing a seriously disabled child. Lastly, we used the adoptee method to study major mood disorders. Our study groups consisted of the relatives of patients with unipolar and bipolar depression; we didn't separate the two diagnoses in those days, and the relatives of a group of normal control adoptees.

TB: What did you find?

PW: We found significantly increased risk of affective disorder only among the biological relatives of the major mood disorder patients, and most striking, a 15-fold increase in suicide in the biological relatives of the adoptees with affective disorders compared to the biological relatives of the normals. This was presumably mediated by mood disorders experienced by the biological parents and siblings of the adopted patients with major mood disorders. We turned our methodology and our population register over to other psychiatrists, who used the adoptee method and the registers to explore genetic contributions to alcohol abuse, criminality, and to psychopathic personality. The results here were more complex. There were environmental contributions to these disorders, in that someone born to a criminal and adopted by a criminal was more likely to be criminal than someone born to a criminal and adopted by a non-criminal. But the major discovery was that there was a genetic contribution to criminality, alcoholism, and "psychopathy." I consider these studies to have done useful work historically. They documented the fact that there was "gold in them there genetic hills." If geneticists approached these disorders with appropriate

methodology, they would be able to elucidate the specific genetic factors that were mediating the phenotype of these disorders. Back in 1967, this was in the distance, and I turned my attention away from adoptive studies in psychopathology to study another interesting area, which I consider to be my second major contribution to psychiatry.

TB: What was that?

PW: The awareness that adult psychiatry could not really explain the etiology of psychopathology very well. I wondered, if one studied children, whether one could learn more about the development of psychopathology. Accordingly, I decided to take a fellowship in child psychiatry at Johns Hopkins, in 1964. The chairman was Leon Eisenberg, who was a critical psychiatric free thinker and who provided a congenial atmosphere. Early in my training, I became interested in a group of children diagnosed with minimal brain-damage who were active, disobedient and oppositional, impulsive, inattentive, did badly in school, had difficulties with their parents, siblings, and peers whose symptoms all but disappeared when given d-amphetamine. Theirs was the most rapid and striking response to drugs that I had and have seen to this day. The only response to somatic intervention comparable to that is ECT in involuntal melancholia. D-amphetamine began to work in 45 minutes, and when continued, the child functioned better than he ever had in his entire life. Mainly, in psychiatry, we try to get people back to the status quo ante, the best they have functioned before their illness, not better than they have ever functioned in their lives. I became interested in the phenomenology of these children and started studying their clinical characteristics. Because I was interested in experimental psychology, I was struck by the similar response of rats and children to dextroamphetamine. D-amphetamine in rats potentiates some of the effects of positive reinforcement, as in the electrical stimulation of the brain, and strengthens negative reinforcement-avoidance behavior, in those which don't learn to avoid punishment in the shuttle box. Given d-amphetamine, most of the non-avoiders who did not learn to avoid punishment do so. It struck me these children were fairly unresponsive to positive reinforcement from their parents and also to punishment, i.e., negative reinforcement. I then became interested in the mechanism of action of d-amphetamine. Since d-amphetamine is an indirect agonist for dopamine and norepinephrine, I hypothesized that minimal brain dysfunction, as it was then called, now attention deficit hyperactivity disorder (ADHD), was mediated by decreased dopaminergic and/or catecholaminergic function. To be immodest, my hypothesis was prescient, because there

have been several meetings at ACNP about the dopamine transporter and the dopamine receptor in ADHD in children.

In 1973, after 11 years at the NIMH, I received a research professorship at the University of Utah; a hard income appointment, which enabled me to do research for 26 years. I had been impressed with the fact that the parents of ADHD children often had problems similar to those of their children. To learn more about this, I began to talk to the parents and asked them, "Did you have problems like Johnny when you were a child?" And, the spouse would say, "What do you mean USED to have problems?" And, then, because of my psychoanalytic training, I'd spend two hours talking to them. Many had symptoms of minimal brain dysfunction, expressed in an adult form such as inattention, hyperactivity, mood lability, overactive responses to stress, disorganization, impulsivity, and hot tempers. On the basis of these observations, I had residents obtain patients from the outpatient clinic who had this group of symptoms. Because ADHD in childhood is a mandatory prerequisite of ADHD in adulthood, and because many of our patients' memories were unclear, we obtained permission to question their parents about their childhood. When parental reports described ADHD behavior in childhood and when the patients had several of the adult symptoms, we diagnosed them as ADHD adults. The next step was to perform a drug trial. Since methylphenidate was the drug of choice for children, in 1976, we did a double-blind crossover trial of methylphenidate and placebo in the treatment of these supposed ADHD adults.

TB: What did you find?

PW: Treatment was very effective. It reduced symptoms extensively and two-thirds were rated as much or very much improved. This was a small sample; one of the problems of interpretation was when you're taking people with a mélange of psychiatric symptoms, and treating them with a euphoriant drug, the results might be similar to those we could have obtained with morphine.

We had to make sure this wasn't the case. So what we did next was treat another sample of ADHD adults with pemoline (Cylert), in a double-blind placebo controlled trial. Now, pemoline is effective in ADHD, but it is not a good recreational drug, and it's insoluble. If you inject it intravenously, all you will get for your efforts is a pulmonary infarct. Our finding using pemoline supported our view that ADHD exists in adults and its symptoms respond to pharmacological treatment with a non-euphoriant drug effective in children with ADHD. After these two drug trials, we initiated a number of studies. First, we decided to replicate our methylphenidate findings with

a larger sample, in which we studied the concentration of the principal metabolite of dopamine, homovanillic acid (HVA) in the CSF of ADHD patients and controls. Our hypothesis, advanced by me in 1971, was that ADHD was produced by reduced dopaminergic activity and that the levels of HVA would be lower in the CSF of patients than in controls. Obtaining a group of a control group of normal adults presented a problem. What we did was to ask the healthy partners of the patients to participate and most of them did. To minimize trauma, we enlisted the participation of the Chairman of the Department of Anesthesiology. Analysis of the CSF found a significant decrease of HVA in the CSF of ADHD patients compared to controls. The clinical findings replicated those of our previous placebo-controlled studies of pemoline and methylphenidate. ADHD patients experienced a substantial and highly significant benefit from treatment. There were other ways I wanted to look at dopamine, and one was administering precursor amino acids: phenylalanine, L-DOPA, and tyrosine. To summarize our results, phenylalanine did nothing and L-DOPA made people cloudy, and produced nausea and fatigue; it did not improve concentration or benefit any other ADHD symptoms. The response to tyrosine was different. After about two weeks, it had a marked beneficial effect. Now, it was an open study, but we had run trials of two other amino acids in which no benefits occurred, so we didn't think the tyrosine effect was a placebo effect. An interesting thing that occurred in the trial was that one patient started getting more and more paranoid. After we stopped the tyrosine the symptom remitted. We had erroneously picked someone with schizotypal personality disorder, who had symptoms in common with ADHD and had given him an amphetamine-like drug which will, of course, increase the severity of paranoia. The other patients showed as much benefit as they had on stimulants, but after about six-weeks they became tolerant, and further increase in the dose of tyrosine had no effect.

TB: But after about two-weeks of treatment tyrosine had a beneficial effect?

PW: Since tyrosine is the immediate metabolic precursor of dopamine, we felt that the results supported that hypothesis that dopaminergic function plays a role in the pathogenesis of ADHD.

TB: You measured HVA in the methylphenidate study but not in the tyrosine study? PW: Yes. As I said, studying ADHD in adults allowed us to get informed consent to perform studies, which would be difficult to perform with children. Among these was the administration of monoamine oxidase (MAO) inhibitors, as a partial test of the dopamine hypothesis. We chose first to study pargyline, which in low dose is a relatively pure inhibitor of MAO-B. Monoamine oxidase B

metabolizes phenethylamine and dopamine. We reasoned that if these were critical neurotransmitters, treatment with MAO-B inhibitors should produce therapeutic benefits in ADHD adults. It did. A problem was that although pargyline was as effective as methylphenidate in some patients receiving low doses, others responded only when we increased the dose to levels where it was probably beginning to inhibit MAO-A as well. So, we decided to perform a therapeutic trial with L-deprenyl, which is also a fairly specific MAO-B inhibitor, and to confine the trial to low doses of the drug. We found that the same percentage of ADHD patients, about two-thirds, manifested much or very much improvement, but they also experienced some subtle dysphoria. None wanted to continue on L-deprenyl, even though their ADHD symptoms were relieved, while many patients chose to continue treatment with pargyline.

TB: Did you measure CSF HVA in these experiments?

PW: We measured HVA only in the methylphenidate study. One important feature of doing invasive studies was that we could obtain informed consent from adults. Of course, we could never have done a lumbar puncture study in children.

TB: You obtained dysphoria with L-deprenyl, which is kind of unique, because one would have expected the opposite.

PW: That's right. I should say something about our experience with methylphenidate and amphetamine in ADHD adults. We continued to treat many of our patients with stimulants and found their symptoms and their social functioning improved. For example, rather than being fired from jobs, they got promoted; rather than dropping out of school, they progressed; difficult marriages and relationships improved. Accordingly, we decided to conduct a one year trial of methylphenidate to determine if we could systemically document these observations. We began with a double-blind crossover trial of methylphenidate and placebo and found, as before, that two-thirds of the patients showed much or very much improvement on the active drug. The effect size was large, 0/8 comparable to 0/3-0/4 in trials of novel antidepressants. The 75% of our sample who showed much or very much improvement on methylphenidate were then entered into a yearlong trial of the drug. We measured the symptoms which characterize adult ADHD, such as inattention, hyperactivity, mood lability, over reactivity, disorganization, stress intolerance, and impulsivity. In addition, we measured social adjustment with the Weissman Social Adjustment Interview and Scale. Symptoms and social adjustment were measured at baseline and at six and

twelve months. There was an 80% reduction in severity of all seven ADHD symptoms. Their average severity was between “not at all” and “slight.” In addition, we found a substantial improvement in social adjustment which measured relationships with his/her partner, children, extended family, work, and economic functioning. Patients improved from “moderate impairment” to “slightly less than good functioning” over the year. The effect sizes of symptom and social functioning improvement was greater than 2. So, we documented systemically what we had noticed clinically, that long-term treatment of ADHD in adults results in much better functioning in all respects. This can be illustrated by one case vignette. This was a 21-year-old woman who entered our study at the suggestion of her social worker aunt. She had had two children out of wedlock in high school, had been using drugs, but had given them up, and was currently living on welfare. During a short term trial, she became very much better on methylphenidate and we continued medication on an open basis. She became interested in getting a general equivalency for her high school degree and attained it. She didn’t like being at home all the time, so she got a part-time job, while her mother gratefully baby sat the children. In a few years, she had a full-time job and was promoted. Then she had the good fortune to meet a nice guy. Luck plays a huge role in human affairs but is never commented on by psychiatrists. He was willing to marry her despite the two illegitimate kids. They had a very good marriage, and she decided she would like to get a college degree. No one in her family had ever gone to college. She entered the University of Utah and graduated with a 3.8 average. In her senior year, she decided that she would like to study cognitive psychology, and she got into graduate school on a full scholarship. This fall she e-mailed me to let me know that she had obtained a second scholarship. I have treated many patients with similar outcomes. While anecdotes prove nothing I wanted to illustrate what an effect size greater than two means in the real world. It’s not the same as a 50% response to an antidepressant drug versus a 35% response to placebo in controlled trials of antidepressants. So I consider my two contributions to have been in the area of minimal brain dysfunction, now ADHD, and the adoption studies of psychiatric disorders. ADHD has now become the disease of the decade and is plastered all over magazines and on the web. I contributed to that explosion, when I wrote the first monograph on minimal brain dysfunction in kids, in 1971, and the first monograph on ADHD in adults, in 1995.

TB: What are you doing these days?

PW: I am in partial retirement in Andover, MA, where I am seeing private patients.

TB: Could I ask you a couple of more questions?

PW: Of course.

TB: It seems you were first to have the idea of using the adoption methodology in the Danish studies...

PW: Yes, but at the same time, so did Seymour Kety and David Rosenthal. Our projects were collaborative. It is amazing.

TB: The research continued over a period of...

PW: About ten years. And then we gave the research registers to other people to do other kinds of research. One of the great joys of my life was working with these two men. Dr. Rosenthal and Dr. Kety treated me as a peer. Dr. Kety was a great man whom I loved and whom I miss very much. Every time an interesting thing happens in the world of schizophrenia, I think I must call Seymour right away, and now I can't; I know what pleasure he would get out of it. Did you know him?

TB: Yes. So you were close to him?

PW: Yes, we were dear friends.

TB: What about the others?

PW: Dr. Rosenthal?

TB: Yes.

PW: I was also very close with Dr. Rosenthal. He mentored me and taught me a great deal of psychology. Just as I was leaving NIMH, he developed rapidly progressive Alzheimer's.

TB: I see.

PW: He died in the 70s.

TB: What about Fini Shulsinger?

PW: Fini Shulsinger is in Denmark and still alive. He is a Past president of the World Health Organization. I saw him several years ago. He is still going strong so far as I know. To repeat his role in our research, Dr. Shulsinger searched through the central registry of all patients in Denmark admitted to psychiatric hospitals with presumably genetic disorders. Fini quickly eliminated those who had multiple sclerosis or epilepsy. He then dictated summaries of all the severe psychiatric disorders. He has a low, quiet drawl in English. I remember sitting in Dr. Kety's office together with Dr. Rosenthal listening to endless audio tapes of Dr. Shulsinger. Dr. Kety

smoked a pipe, and in that era I smoked cigarettes. We'd listen to three or four hours of Fini's tapes in English with a Danish accent, in a smoky room. He was an invaluable collaborator. Without his participation we could never have conducted our studies.

TB: What about Jacobson?

PW: I don't know what happened to Dr. Jacobson. I believe he is still alive and functioning well.

TB: After the adoption studies, your research interest moved from schizophrenia to...

PW: To bipolar disorders. The important thing is we and others, using our method, showed a genetic contribution to a variety of psychiatric disorders. This was different from twin studies, in which one could account only for genetic factors. Our method measures the amount of variance due to genetic contributions. In the case of schizophrenia, we could find no evidence supporting the role of non-genetic familial factors in the development and degree of schizophrenic symptoms. That set the stage for the molecular geneticists to do their stuff, which in 1967, wasn't much.

TB: And the adoption studies showed that in certain disorders environment also plays an important role?

PW: Right. As this particular ACNP meeting has shown, the interaction of genetic factors with early environment can actually change gene expression in some disorders. Our research influenced the whole field of psychiatry and produced a sea change. I hope this does not sound like an arrogant statement.

TB: Your findings in the adoption studies certainly influenced the whole field, and you also pioneered in ADHD in adults.

PW: Yes, it has. And I can't figure out how I did this, because I still think of myself as 21 years old; not 68 giving an oral history because I'm an aging neuroscientist.

TB: You are in partial retirement you said.

PW: And seeing patients which I enjoy a great deal, mainly on a consultation basis.

TB: You trained many people. Would you like to mention just a few of them?

PW: Dan Safer in Baltimore. He has done a lot of creative work on ADHD. Ron Reider worked with me at the NIMH; he is head of psychiatric training at Columbia. Jim Harris is a neuroscientist at Johns Hopkins, who has done basic work on all aspects of Lesch-Nyhan syndrome and has written a seminal two-volume text on developmental psychopathology. He is a multi-faceted man who writes the commentary on the paintings the *Archives of General Psychiatry* uses on its cover.

TB: When did you become a member of ACNP?

PW: I think, 1975, I'm not sure.

TB: And you have been active in the college? Did you serve on any of the committees?

PW: I've always abjured sitting on committees and avoided department chairmanships.

TB: So you did what you liked to do? You were involved in research and teaching mainly?

PW: Yes, and also treatment throughout. I was always in practice. I can spend only so much time doing research. Practice in the real world that has been both a basis for my research and a gratifying and rewarding activity.

TB: On this note we should conclude this interview with Dr. Paul Wender. Thank you, Paul for sharing this information with us.

PW: Thank you.

65. RICHARD J. WURTMAN

TB: We are at the 45th Annual Meeting of the American College of Neuropsychopharmacology at the Acapulco Princess Hotel in Acapulco, Mexico. It is December 12, 1998, and I am going to interview Richard Wurtman⁶⁷ for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let's start from the very beginning. If you could tell us where you are from, where were you brought up, something about your education, and how you got involved in psychopharmacology?

RW: I was born in Philadelphia and went to an excellent public school, Central High School. After which I went to college at the University of Pennsylvania. At that time, I thought of myself as a pre-law student. My father was a lawyer, I was a debater. Some people say I am still a debater. I wanted to do law, I thought I liked it. And, I was a philosophy student in college. I got a master's degree in Philosophy of History and this did have an impact on what I've done since. But, in my last year of college, I decided I wasn't sure I wanted to be a lawyer. I met a student at Harvard Medical School, who convinced me if I went to medical school I could do two things; I could be a medical scientist and discover things, or I could make sick people feel better. For one reason or another, I decided at the end of summer that I wanted to be a doctor instead of a lawyer. This caused a small amount of chagrin in my family. My poor brother had to become a lawyer instead. I spent my last year in college taking a course or two in chemistry and zoology. You could do that and still get into medical school in those days. Then, I applied to a couple of medical schools and got into Harvard. I left Philadelphia, went to Boston, and haven't left since except for four years at the NIH. I told myself I wanted to work on the mind/body problem. Coming from philosophy I wanted to understand how the brain generated the mind. My son is a doctor and when I told him that he said, "Gee dad, what went wrong." But one still tries and I'm delighted how recent advances in clinical psychopharmacology bring us closer to understanding mind-brain relationships. With this commitment to the mind/body problem, I wanted to initiate research as soon as I started in

⁶⁷ Richard Wurtman was born in Philadelphia, Pennsylvania in 1936. He received his M.D. from Harvard Medical School in Boston, Massachusetts. After clinical training at the Massachusetts General Hospital in Boston, Massachusetts and research training at the Intramural Research Program of the National Institute of Mental Health in Bethesda, Maryland, he joined the faculty of the Massachusetts Institute of Technology in Boston. He was interviewed in Acapulco, Mexico on December 12, 1998.

medical school. I was lucky; Harvard had just started a program which would encourage medical students to do laboratory research, and so by the end of my first year, I had started a research project. While I was in medical school, I spent almost as much time on research projects as on becoming a doctor. The first research project was related to what followed. It was with a professor of cardiology, Mark Altschule, who believed that schizophrenia was a disease of the pineal gland.

TB: What was his argument for that?

RW: It's the only unpaired midline structure in the brain, so it must do something fundamental. Around this time, a blood test for schizophrenia had been published in the journal *Science*. It was the Akerfeldt test. Altschule thought he could cure schizophrenia by giving patients extracts of cow pineals, so he hired me and one of my classmates to do the Akerfeldt test on people before and after they received pineal extracts. His idea was he should be able to show that not only did the extracts cure schizophrenia behaviorally, but also biochemically.

TB: Was this in the late 1950s?

RW: This was about 1957 or 1958. The one good thing that came out of that summer was that I became interested in the pineal and a few years later, while I was still in medical school, started doing research on what happened to rats if you took out the pineal or administered pineal extracts. So by the time I graduated from medical school, a corpus of publications had appeared, describing effects of pinealectomy or the extracts. Just around this time, Aaron Lerner at Yale University discovered melatonin in similar pineal extracts. So, one of the first things I did when I got to the NIH two years later, was discuss this with my very good friend, and kind of uncle, Julius Axelrod. Together we showed that the active pineal principle which affected rats was melatonin. Our findings that it promotes sleep, and that its deficiency can lead to insomnia in the aged, were not made until many years later. This led to our discovery that melatonin is actually a hormone in mammals. Melatonin had been discovered based on its action to lighten the color of tadpoles' skin; its function in mammals was not known. So, something good came out of that first summer in medical school. I enjoyed being in medical school but I also enjoyed the role of researcher, creating much confusion concerning my career goals. A nagging question was, "Do I want to be a doctor or do I want to be a scientist?" At Harvard, at that time, there was this marvelous myth that the ideal thing for all graduates would be one-third research, one-third teaching, and one-third seeing patients. I looked around for a role model, somebody who was successful in doing all three.

TB: Did you find one?

RW: There were many people trying to do all three, but I could find no one who came across as successful. So, I decided I wouldn't try. But what then should I choose? I didn't know. So, I went to the Massachusetts General Hospital as an intern and a resident for a few years. I really liked taking care of sick people, but then, I went to the NIH and spent two years as a fellow with Julie Axelrod. And I didn't just like that, I loved it! It was an incredible eye opener. Partly, of course, it was Julie's extraordinary gift, his personality and his excitement about science and capacity to translate a complex question into simple experiments. At the end of my two years at the NIH, Seymour Kety, who was running the laboratory, and Julie invited me to stay permanently. But there was no room at that time, so they said the NIH would send me away for a year to any place I'd like to go. I still thought perhaps I could integrate basic science and clinical medicine. In fact, that's what I was going to do later on, but didn't know then. So I went back to the Massachusetts General Hospital (MGH) for a year in 1964-65, as a clinical Fellow in Endocrinology and Neurology. It was a good year; the experience convinced me I wanted to be a scientist. At the end of that year, in 1965, I moved back to Bethesda, planning to spend the rest of my life at the NIH. But, I spent only two years before going to MIT. And I've stayed at MIT since. My year at the MGH in 1964-1965 was good for me because I happened to make a clinical observation that paid off. There was a woman seen by the Endocrinology Group who had a pituitary infarction during the process of having a baby. It happens in some people. So, her pituitary gland didn't function. Her major symptom was that sometimes two, three, or four hours after eating she had seizures that were associated with hypoglycemia. Nobody understood why pituitary insufficiency might lead to hypoglycemia after eating. People thought it might be via deficiencies in ACTH or gluconeogenesis, but that process takes too long to become manifest so soon after eating. I got the idea that since the fast process of raising blood sugar after insulin release involved adrenaline, perhaps the pituitary might have something to do with the control of adrenaline production. When I went back to the NIH, my associates and I took out the pituitary from rats and dogs and showed that doing so profoundly impaired the capacity of the adrenal gland to make adrenaline and release it into the blood stream. So, I was lucky. By that time, I had been at the NIH for two 2-year periods. In the first two years with Julie I'd shown that melatonin was a hormone and that the synthesis of melatonin was controlled by light and darkness, as well as by

the sympathetic nerves. And that the production of melatonin exhibited a daily rhythm. We wrote a lot about the daily rhythms and helped to popularize that field. And in the second two-year period, I asked myself the question why God put the adrenal medulla inside the adrenal cortex and answered it by showing that the pituitary stimulates the cortex to make cortisone which is selectively delivered to the medulla and controls its production of adrenaline. So by 1967, I was known for having discovered two sets of things. I was becoming a 'hot commodity' among academic recruiters.

TB: Why did you pick MIT?

RW: One reason I picked MIT was that a Washington-area colleague, who was probably the world's greatest neuroanatomist, Walle Nauta, had moved to MIT a year earlier to join its neuroscientists. Also, I had a good offer from MIT and liked living in Boston. By 1967, my formal education was over; it included components of clinical medicine, but larger components of basic science. I went to MIT to establish and direct my own laboratory. MIT is a great place. It operates as a large number of independent systems. We have departments that give degrees, but for the most part, individual professors are nearly completely independent. I have now been at MIT for more than twenty-five years. Hundreds of students and fellows have gone through my laboratory. I've had a number of opportunities to leave MIT but never wanted to. I plan to be there until I'm a hundred if they'll have me.

TB: What have you been doing at MIT?

RW: Basically I do two things. I try to discover new facts about how the body works normally, and when it doesn't work, using molecular and neurobiologic techniques, I apply what I find in basic research to humans. I try to determine whether or not things we observe in the laboratory occur in people. We have a clinical research center at MIT, one of the seventy clinical research centers in the country funded by the NIH, the other sixty-nine being, for the most part, in university hospitals. It was established at MIT before I arrived, to facilitate translational research. A large part of my time is spent doing that sort of research. For example, we discover in rats that giving melatonin has an effect, so then we look in people to see whether it does the same. Then we look for a use for its effects, like treating insomnia. The other thing I do is teach. I do a lot of classroom teaching, which I enjoy. I also do a lot of apprenticeship teaching. Our major output is publications and talk about publications. The other output is "translation," converting laboratory discoveries

into something clinically useful. I do this with companies, regulated by the government. In the course of implementing this interest, I've had to learn disciplines and approaches I wouldn't have thought necessary, for example patenting. If the inventor doesn't patent a discovery no one else can, and it probably will never be developed. I discovered this in a very unfortunate way.

TB: How?

RW: One of my students, John Fernstrom, and I discovered in the early 1970's, that the amino acid tryptophan, given in very low doses, could increase brain serotonin. We speculated and then showed that this relationship could be used for influencing a variety of behaviors that depend on serotonin, like treating insomnia. We wrote a series of three articles in *Science*, and two in the *Scientific American*, and papered the walls with our discovery. I assumed this would naturally lead to tryptophan being a good and useful product. Five or six years later, I realized that this had not happened; no major company had developed tryptophan as a drug in the United States. But since tryptophan worked, and everybody knew it worked, companies were selling it as a dietary supplement without FDA approval. Even though we all love to hate the FDA, there are some situations where the FDA is quite essential. Since there was no regulation for marketing tryptophan as a dietary supplement, there was also no regulation of its purity. So, in the 1980's, a batch of impure tryptophan was introduced into America from a Japanese company. They developed a new microorganism capable of making it from aniline, and the process was very efficient. So, they lowered the price and took over the entire market for tryptophan in the United States. The trouble was the drug produced eosinophilia in some patients. Had tryptophan been under FDA regulation, the company would have had to do phase one studies on the newly synthesized tryptophan, and some of the subjects would have developed eosinophilia. This would have been evidence of an allergic type reaction, which would have caused the product to be withdrawn. Since there were no such studies, large numbers of Americans took the impure tryptophan without knowing about its toxicity, and forty-five died as a consequence of a new syndrome, the eosinophilia myalgia syndrome. And I felt a little bit responsible; if I'd done what I should have done, if my university had patented tryptophan for insomnia and controlled its use by companies that licensed the patent, this wouldn't have happened. Anyhow, I'd discovered the need to patent discoveries by the mid 1970's. I still don't patent anything, but MIT almost always patents discoveries that might lead to products. For example, something my wife and I discovered; my wife is my close collaborator in

a lot of ways. She's a cell biologist, whose fundamental work is in nutrition and obesity. She has a PhD, not an MD, but she listens to her patients and discovered the phenomenon of carbohydrate craving. There are very many patients, who get obese, not because of what they eat at mealtime, but because they overeat large quantities of carbohydrate-rich snacks. These snacks tend to be fat-rich, providing about 1500 calories a day, and even more, if the person suffers from seasonal depression. And they get fat. In 1970, with John Fernstrom, I found carbohydrates increased brain serotonin levels. So we made the hypothesis that these people were overeating carbohydrates to increase their brain serotonin because that made them feel better. And that is what patients said. If that's the case, the way to ameliorate their obesity is either to give them carbohydrates via foods that lack fats, and this works for some, or find drugs that do the same thing to brain serotonin that carbohydrates do. That was the origin of the concept that serotonin, and not dopamine or amphetamine in the brain, is the right target for antiobesity drugs. To make a very long story short, we discovered that dexfenfluramine, a serotonin agonist, could be highly effective in treating obesity, particularly obesity associated with carbohydrate craving.

TB: Can you identify the obesities which are associated with carbohydrate craving?

RW: One example is seasonal depression. There are people with seasonal depression who put on 15 pounds every winter and take off 10 every summer. There are women overeating with the premenstrual syndrome or when trying to stop smoking. There are also people who have stress induced overeating. We worked with a French company, Servier, to develop dexfenfluramine as a treatment for this kind of obesity and the substance was ultimately marketed under the name of Redux. It was sold in the United States for about a year but was withdrawn about two years ago, because it became confused with Fen-Phen. Fen Phen actually consists of three chemicals; dexfenfluramine, L-fenfluramine, and phentermine, an antidote to the side effects of Lfenfluramine, a dopamine receptor antagonist. Phentermine turns out to be a potent MAO inhibitor and you're not supposed to give an MAO inhibitor with a serotonin-uptake blocker like dexfenfluramine, Prozac (fluoxetine), Zoloft (sertraline), or Paxil (paroxetine.). The trouble was that phentermine was not labeled as an MAO inhibitor. A bunch of us are trying to persuade the FDA it should require that phentermine be labeled as an MAO inhibitor. So, Fen-Phen, in a certain number of people, by blocking both the serotonin uptake into platelets and the enzyme MAO, allowed plasma serotonin levels, to rise transiently to very high levels, which produced vascular

lesions in some people. Dexfenfluramine doesn't do that by itself, nor does Prozac, Zoloft, Paxil, and other serotonin reuptake inhibitors. They do it only when they are taken with an MAO inhibitor like phentermine.

TB: Do you think dexphenfluramine might be revived?

RW: I don't think dexphenfluramine will come back, but there will be other similar drugs that either release serotonin or that act on the right receptor in the brain to suppress eating. Anyhow, dexfenfluramine, Redux, was for a while a great success story. Here was a university discovery and a university patent that was marketed and used in the treatment of a large number of people. There are very many who need treatment with a serotonergic drug. One example might be a 50-year-old man, who weighs 270 pounds, has hypertension and diabetes, and can't stop eating. He will die if he's not treated. So I hope we get other drugs like dexphenfluramine. We've had a few other successes that relate to the use of drugs that were discovered in our laboratory and patented by my university. Universities, in general, cannot come up with new compounds; we're not drug companies and don't have the medicinal chemists to generate the new compounds. But what the universities are good at doing is discovering additional, off-label uses for old compounds and then trying to get the drugs developed for those uses. We had, a sort of, triumph about three or four weeks ago. My wife had the idea that women with pre-menstrual syndrome gained weight because they developed carbohydrate craving.

TB: Why do women with pre-menstrual syndrome develop carbohydrate craving?

RW: They develop carbohydrate craving because they feel lousy. They're angry; they're depressed; they're miserable and they've learned that by consuming carbohydrates they can transiently ameliorate these feelings because the carbohydrates increase brain serotonin. There are a couple of ways to treat this. She invented a carbohydrate based food packet, called PMS Escape, which is still being sold, that helps a lot of women. It's giving the carbohydrates without fat, so the women get increased brain serotonin but don't get the increased waistline. Together we showed that a variety of serotonin drugs could also be used, specifically, to treat the premenstrual syndrome. So MIT went ahead and patented the use of these drugs for treating PMS. One of them was Prozac. Lilly licensed that patent and did large-scale clinical trials. On the basis of their findings, a few weeks ago, an FDA Advisory Board unanimously approved our invention, the use of Prozac (now "Sarafem") for treating pre-menstrual syndrome. It's safe to anticipate that early

next year, Lilly will be marketing Prozac, under its new name, for this MIT discovery. And maybe, there will be other drugs in the patent, too. Another compound we don't know the outcome on yet is for the treatment of stroke.

TB: What kind of compound is that?

RW: It's a compound that acts directly on the brain, as opposed to the clot busters like TPA. When you get a thrombotic stroke what happens in the next three or four days causes a 75 or 100 percent increase in the size of the affected area. The dying necrotic tissue releases unsaturated fatty acids, like arachidonic acid, which become auto-oxidized or diverted to form thromboxanes and prostaglandins, which diffuse around the dead tissue, and extend the affected area. So, one theoretical goal of stroke therapy is to invent a drug that either blocks the release of these compounds or blocks their conversion to toxic metabolites. We showed in the laboratory our compound could do that. There are three doctoral theses written by our graduate students showing that if you present the brain with increased amounts of phosphatide precursors, such as choline and cytidine, cytidine becomes CTP, which is needed to make phosphatides, and choline becomes phosphocholine, enhancing the formation of phosphatidylcholine and other phosphatides.

TB: Why is it good to enhance the formation of phosphatides?

RW: Making more phosphatides is good for two reasons. Firstly, the last step in making phosphatides involves adding diacylglycerol, much of which contains arachidonic acid. You can show in experimental preparations that giving a source of choline and cytidine decreases the level of free arachidonic acid, and, thereby, the size of the stroke. The second thing is that a stroke kills a bunch of cells, damages a much larger number, so the brain needs to regenerate those axons. There's much more optimism now about neuronal regeneration in the brain than before. Since phosphatides are by far the major component of membranes, enhancing phosphatide synthesis should enhance membrane formation and accelerate recovery from stroke. The way we picked to provide choline and cytidine was to use an old, controversial compound, citicoline. Citicoline has undergone patient Phase Three clinical trials and awaits complete analysis. Another thing we invented is the use of melatonin to promote sleep. It's another MIT patent, based on studies done in our clinical research center, which followed decades of studies done on rats, showing nocturnal release of melatonin. It's had a checkered course, because melatonin unfortunately is regulated as a dietary supplement.

TB: Why is melatonin qualified as a dietary supplement?

RW: Congress passed the Dietary Supplement Act, in 1994, which labeled certain categories of compounds as dietary supplements. So, vitamins, minerals, herbs, amino acids, anything that is present in food, was declared a dietary supplement regardless of safety. There is a tiny amount of melatonin in food; thirty bowls of rice or 120 bananas give you one dose of melatonin. No food has ever been shown to elevate plasma melatonin levels. But on that basis, melatonin is called a dietary supplement. Since it is called a dietary supplement, any company can sell it in health food stores in any dose they want with no evidence of purity or efficacy. And, that's happened. The MIT patent is on the use of melatonin doses up to a pharmacologically appropriate level, usually 0.3 mg, and it's not a good idea to sell higher doses. People get nightmares then. They get receptor desensitization; receptors stop working. So, what I've learned is that if you want to take things out of the laboratory, it's not enough simply to have something that works. That's the starting point. You also have to work through, with your university, the patent situation, and then you have to find a licensee that will do the large-scale clinical trials and invest in the toxicity studies. Then, the FDA will approve this sort of thing. Finally, as we learned from Redux, one has to hope the compound doesn't have some unanticipated side effect when combined with another drug. But, it's well worth doing this sort of work. And I'm glad to see that numerous other investigators in universities are trying to convert basic science findings to clinically useful products.

TB: In so far as your own work is concerned, how would you describe your activities?

RW: I do three things. I run a basic science laboratory and I direct the clinical research center, where we do studies trying to see whether our findings in the lab also work in people. And I'm interested in translation, in taking the discovery out of the laboratory by developing products that might be useful for people. Is that the longest answer to a simple question that you've ever had?

TB: It certainly answers the question. Am I correct that the starting point of your research at MIT was your interest in tryptophan?

RW: That's right. Do you want to know the history to that?

TB: Yes.

RW: It's a wonderful story. When I was at the NIH, in my second period there, working with Julie Axelrod, we got interested in circadian rhythms. Why? Because, the pineal released melatonin at nighttime and we thought we'd like to have something we could measure in rats to

indicate whether or not melatonin has an effect on the circadian rhythms. We knew that adrenal cortisone manifested a circadian rhythm, and so, I decided to try to set up an assay for corticosterone in the rat, define that rhythm, and see whether melatonin affected it. At that time, the only assay that could be done in a regular laboratory for corticosterone was a fluorescence assay that was very difficult to do. So Julie and I decided that instead of looking at corticosterone, we should look at something controlled by corticosterone that might be measurable. There is an enzyme in the liver, called tyrosine transaminase that can be induced by corticosterone. So I thought, let's see if there is a rhythm in tyrosine transaminase, and if so, whether it parallels the corticosterone rhythm. We took rats and measured their tyrosine transaminase activity at different times during the day and night, and discovered there is a rhythm. Assuming the rhythm was due to corticosterone, we thought if we removed the adrenals that would block it. It didn't. By this time, I'd moved to MIT and got interested in what was causing the rhythm. I was very fortunate. Down the hall from me was an extraordinary scientist, Hamish Munro, who was an enormously well regarded student of nutrition. Through Hamish, I learned nutrition could be relevant to generating rhythms. For instance, the amount of tryptophan and other amino acids delivered to the liver controls whether it's making protein or not. We discovered the rhythm in tyrosine transaminase depended on what the rat ate. If the rat consumed food that contained protein, then amino acids got to its liver and turned on protein synthesis. So, we learned that eating controls the rhythm in tyrosine transaminase synthesis. Since tyrosine transaminase transmits the amino acid tyrosine, we hypothesized there might also be an inverse rhythm in the amount of tyrosine. After all, if you have more of an enzyme you ought to have less of its substrate. So, we started doing studies on rats to see whether there is a daily rhythm in tyrosine synthesis. Yes, there was. Since tyrosine is a substrate for tyrosine transaminase, but tryptophan isn't, there should not be a rhythm in tryptophan levels. We took people at our clinical center and collected their blood around the clock and found there were rhythms in the levels of almost all of the amino acids. Here again, we did the experiment to test an erroneous hypothesis, and in the process, found something perhaps more interesting. We discovered all amino acids undergo daily rhythms, including tryptophan. I had previously done some work on serotonin and knew the enzyme that converts tryptophan to serotonin exhibited low affinity for this substrate. At normal tryptophan concentrations this enzyme was not doing very much, because only a little bit of it was saturated. It seemed to me that

if there were daily rhythms in blood and in brain tryptophan there might also be changes in the production of serotonin. After I moved from NIH to MIT, I had an excellent graduate student, John Fernstrom, who worked with me on it. We found that very small changes in brain tryptophan levels, produced by giving tryptophan, could cause major changes in serotonin synthesis. So why not give a high protein meal, since protein contains tryptophan. We also thought if we lowered blood tryptophan levels by giving insulin, this should interfere with brain serotonin synthesis. So, we gave animals insulin injections, lowered blood tryptophan, but lo and behold, brain tryptophan levels and serotonin synthesis increased. This seemed very strange, so we decided instead of giving insulin, we should give the animal carbohydrate to make it secrete its own insulin. Rats eating a carbohydrate meal showed the same response as those given insulin; it raised brain tryptophan and serotonin synthesis. What this suggested was that the amount of tryptophan that gets into the brain doesn't just depend on blood tryptophan, but also on other amino acids that compete with tryptophan for entry to the brain. What actually happens is that insulin pushes other amino acids, such as leucine, isoleucine, and valine into muscle, where they're metabolized. The effect of carbohydrate is to cause blood tryptophan levels to decline a little, but levels of its competitors to decline a lot, so even though there's no tryptophan in dietary carbohydrates, there's a tremendous increase in the amount of tryptophan getting into the brain, and a corresponding increase in serotonin synthesis. Conversely, if the animal had a protein meal, blood tryptophan does rise a little bit, but levels of the competitors rise much more.

TB: Why?

RW: Because only one percent of most protein is tryptophan, whereas 25 percent is tryptophan's competitors. So, there was this beautiful paradox: eating a meal that contained no tryptophan, a carbohydrate meal, raised brain tryptophan and enhanced serotonin synthesis, whereas eating a meal that contained tryptophan, because it contained protein, had the opposite effect. After struggling with this for a couple of years we realized our findings indicated that serotonin neurons have a special capability. They can, on-line, monitor changes in plasma composition generated by eating and report to the brain what you're digesting, whether those foods are principally carbohydrate or principally protein. And, the brain uses this information.

People from all cultures, unless they're limited by poverty, have about 13 percent of their calories as protein and eat about 4 or 5 times as much carbohydrate as protein, however, they aren't aware they're doing so. People think they're picking food, but they're also picking nutrients.

TB: How does the brain know what we are eating?

RW: The brain knows by monitoring plasma amino acids, levels of which are changed selectively by the composition of the food. Later on, my wife Dr. Judith Wurtman, discovered the phenomenon of carbohydrate craving. People who overeat carbohydrate-rich, protein-poor foods or snacks, do so because it makes them feel better, less depressed. By the way, serotonin is involved in depression, besides control of what's chosen to be eaten.

TB: Your studies with tryptophan started your research at MIT, but the whole story really began with your interest in the pineal gland and melatonin. Your findings seem to suggest that the organism regulates its nutrient intake.

RW: In most cultures, even cultures of poverty where people eat combinations of beans and rice, they consume enough protein and carbohydrate. What people of poverty tend to have least is fat. Fat is very expensive. You may have to go kill an animal to get it. There seems to be no brain neurochemical system that monitors body fat composition and no central regulation of fat intake. People like fat, it has a good taste. So the desire for fat is based on taste and not any central neurochemical effect. During our evolutionary history, fat was not something people could count on having. People could always have their beans, rice, and vegetables to provide carbohydrate and protein. But not so readily fats.

TB: Would your findings regarding the net effect of eating carbohydrates or protein on brain tryptophan and serotonin synthesis imply that if tryptophan is used for insomnia, it must be given in a small dose to be effective?

RW: That's right.

TB: Are we talking about 500 milligrams or so?

RW: In fact, 250 would have been adequate. In terms of utility, what we found with tryptophan, we are finding also with melatonin. We've just finished a study with melatonin which relates to this. We took a large number of older people with or without insomnia and measured their plasma melatonin levels during the night and during the day. Our findings confirmed what we and others had shown, namely that as you age, nocturnal plasma melatonin levels decrease from 100 to 150

picograms per ml in 20 year olds to perhaps 30 to 50 in people over the age of 50; melatonin levels decrease regardless of whether or not the person had insomnia. Some exhibit insomnia whereas others do not. The nature of the insomnia in aging is not trouble falling asleep; they tend to fall asleep early, because they're exhausted from not having slept well the night before. The problem is staying asleep or awakening too many times. We gave these people three different doses of melatonin, 0.1 mg, 0.3 mg, or 3.0 mg, and found all of the doses improved sleep, but the most effective dose, which brought them up to normal sleep, was the dose that raised nighttime plasma levels to what they are in young people, 0.3 mg. given orally at nighttime. Giving 0.3 mg to older people with insomnia brings sleep efficiency back to normal but has no effect on people who already sleep normally. Nothing is broke in them, so there is nothing there to fix.

TB: Are you suggesting melatonin in the dose of 0.3 mg at bedtime for the treatment of insomnia in the elderly?

RW: Yes, and not in the 10 to 20 times higher doses commonly sold in health food stores.

TB: Are you suggesting for insomnia, tryptophan in a dose of 250 mg for the young, but melatonin, in a dose of 0.3 mg for the old?

RW: That would be perfectly rational.

TB: Am I correct that the development of dexfenfluramine was based on the notion that obesity is the result of a kind of depression in which people, without being aware of it, try to increase their brain serotonin by consuming excessive amounts of carbohydrates?

RW: Yes. Obesity is a heterogeneous disease, but one large subset includes such people. When dexfenfluramine was available it worked in 79 percent of obese people, and this included many who did not have that kind of depression; so it's apparent that serotonin also has an additional role in eating. It's a major satiety factor. But we were able to compare the responses to dexfenfluramine of obese people, with or without carbohydrate craving, in a large study in the Netherlands and found that carbohydrate cravers invariably had an even better response to the drug than the non-carbohydrate cravers. So, you're right.

TB: Was dexfenfluramine tested in the treatment of depression?

RW: It was tested in seasonal depression. The reason it was not tested for depression, in general, is that the companies that marketed it wanted to get one indication clearly established before looking at another. That was unfortunate, because it could have been tested in a variety of other

circumstances. For example, when women stop smoking, what's the main reason they start again? They get fat. Why do they get fat? One thing nicotine does is to act on raphé neurons to release serotonin. So, when they withdraw from nicotine, they release less serotonin and the person selectively overeats carbohydrates, becoming a "carbohydrate craver." It makes very good sense to treat these people with an agent that releases serotonin.

TB: Are you suggesting 5-HT_{2c} agonists should be tested in the treatment of nicotine withdrawal?

RW: That's right.

TB: You have a clinical unit; why are you not doing it?

RW: There aren't any 5-HT_{2c} agonists available, to my knowledge. A number of companies are working on such agents and finding they're safe enough, so they could be tested. I'd love to test these drugs. When Redux was available, my wife and I used it as a probe to find out whether brain serotonin is involved in a variety of conditions. For example, PMS and smoking withdrawal; there might well be additional clinical situations that could benefit from a 5-HT_{2c} agonist. Parenthetically, one of the great things about psychopharmacology, more than any other field of medicine, is how people have taken advantage of the existence of drugs developed for one purpose, to find entirely new uses, extending our knowledge of the chemistry of the brain. There are many examples. I wish other aspects of medicine were as successful as psychiatry and psychopharmacology have been.

TB: After discovering the therapeutic potential of tryptophan and melatonin in insomnia, and dexphenfluramine in obesity, you also discovered the therapeutic potential of citicoline in stroke. I think citicoline is sold in Italy and possibly in some other countries.

RW: Yes, citicoline is sold in some countries. Once we found out serotonin synthesis is controlled by the amount of tryptophan consumed, because the key enzyme, tryptophan hydroxylase, is a low affinity enzyme, I started wondering whether there might be other neurotransmitters or brain chemicals, whose synthesis is also are controlled by the availability of precursors. The obvious other neurotransmitter to consider was acetylcholine.

TB: Why?

RW: Choline acetyltransferase, CAT, is also a very low affinity enzyme and it was known for years, based on in vitro studies, that the amount of acetylcholine one makes could be controlled by the amount of available choline. So, a graduate student and I did some studies to see whether

the availability of choline within its normal range affects brain acetylcholine synthesis; we found that it did. Our findings were quickly confirmed by many other people. So, this got me thinking about choline. I realized that just as most of the tryptophan in the body doesn't go to make serotonin, it goes to make protein, similarly, most of the choline in the body doesn't go to make acetylcholine. Most of it goes into making membranes. At that point, one of my graduate students became interested in the relationship between choline availability and membrane biosynthesis and showed that production of phosphorylcholine, the first step in acetylcholine synthesis, goes up or down depending on the availability of choline. I was deeply interested in Alzheimer's disease about twenty years ago with a colleague and friend, John Growdon, who was head of the Alzheimer Unit at the Massachusetts General Hospital. We both became interested because, just around that time, two English groups had discovered there was a selective reduction in acetylcholine levels in the brains of people with Alzheimer's disease. We wondered perhaps just as giving L-DOPA can replace deficient dopamine in Parkinson's, maybe giving choline would replace deficient acetylcholine in Alzheimer's. It didn't work, but it did get us into Alzheimer's disease research.

TB: But citicoline, as you mentioned it before, seems to be working in stroke, right?

RW: It does seem to be working because there's a clearly defined chemical mechanism involved. In stroke one wants to remove the free arachidonic acid liberated from the infarcted tissue, and citicoline does that. It pushes it back into membrane by incorporating it in phosphatides. The same thing may be true with brain injury of any type, with motorcycle accidents, for example.

TB: How did you get from the treatment of stroke to the treatment of Alzheimer's disease?

RW: We began organizing a series of meetings every two years, the so-called Zurich meetings on Alzheimer's disease so we could learn more; the next meeting will take place in February. They involve about one hundred participants, and a lot of information is transferred. At one of our meetings, I was visited by somebody from a Spanish company that sells citicoline, and he told me he was aware of the work we had done on choline, acetylcholine, and phosphatide synthesis and wondered whether I might be interested in finding out if citicoline also affects acetylcholine or phosphatides. He also told me his company was selling this compound in Spain and elsewhere but people laughed at it and called it an expensive placebo. I couldn't dismiss the possibility there might be something to citicoline, so we started doing research. The first thing we discovered was

the substance breaks down immediately and totally in the body. People had been speculating that if one eats it, it goes right into the brain. This does not happen, it's totally metabolized. But what it does do is raise blood levels of choline and cytidine, at least in animals. In people this is different; it raises blood levels of choline and uridine. The uridine then gets into the brain and is converted into UTP and to CTP. After we found citicoline is broken down completely, we did studies on cultured cells, then on brain slices, and finally on whole rats which showed if one increased choline and cytidine levels, one actively promoted membrane biosynthesis. We took rats or mice and fed them for six weeks on a diet enriched with citicoline. Then, we removed their brains; measured the amount of phosphatidylcholine per cell, and found it went up about 15 percent. So, the joke is, if you want a fat brain, all you have to do is eat citicoline for six weeks in a very large dose. Just as giving tryptophan increases serotonin synthesis, so also, choline affects acetylcholine synthesis. This algorithm also applies to tyrosine. Tyrosine can affect catecholamine synthesis. This is another story. Are you interested?

TB: Of course. Please elaborate.

RW: Tyrosine hydroxylase, the rate-limiting enzyme in catecholamine formation, is more complicated than tryptophan hydroxylase and choline acetyltransferase, in that if a catecholamine releasing neuron fires, tyrosine hydroxylase becomes phosphorylated and its kinetic properties shift. When it's not phosphorylated, the rate limiting factor in hydroxylating tyrosine is the level of a cofactor, tetrahydrobiopterin, but when the neuron fires and the enzyme becomes phosphorylated its affinity for the cofactor goes up two hundred fold, and now the activity of the enzyme is limited by the availability of tyrosine. One can demonstrate this by doing something that makes a certain set of catecholamine neurons fire more rapidly. For instance, after destroying 80 percent of the nigrostriatal neurons, the surviving 20 percent will fire more rapidly, becoming critically dependent on tyrosine levels. One can destroy 80 percent of the neurons on one side of the brain and not destroy any on the other side before giving the animal tyrosine, which is distributed everywhere in the brain. On the side where neurons have been destroyed, giving tyrosine doubles dopamine release, whereas on the other side, where the neurons are intact, it has no effect on dopamine release. We've not tried to apply these findings. We've not done enough work to try to apply these findings in humans, because the treatment of Parkinson's disease has moved ahead of us. We did some small studies in Parkinsonian patients and saw effects, but they

weren't as good as L-DOPA's. Somewhere down the line, there may be a circumstance in which we can take advantage of tyrosine in treatment, too.

TB: Am I correct that you have been instrumental in the discovery of a therapeutic indication for at least four substances?

RW: Actually, there's a few more. There's tryptophan, which has not become a drug because MIT didn't patent it, unfortunately. Then, there is dexfenfluramine, which did become a drug but is no longer. There's one substance that my wife did, based on our work. It's called PMS Escape, a mixture of carbohydrates that increases brain serotonin. It's currently been marketed. There's the recent FDA approval of fluoxetine for treating PMS, called "Sarafem." And there's melatonin for the treatment of insomnia. As long as, in America, melatonin remains a dietary supplement, I'm not sure what to do with it. It's very difficult to get a company to invest and develop it in the United States, so I've turned my attention to Europe, where it's still a drug. I'm hoping a company can be found in Europe that will make a drug out of it.

TB: And, what else?

RW: Some years ago, we took blood from people running in the Boston Marathon, before and after, and measured choline in it. Then, we did the same on people swimming long distances and basketball players and found all of the endurance exercises deplete plasma choline. It goes down 40 to 50 percent, thus suppressing acetylcholine release at the neuromuscular junction. I suspect this may be why runners talk about hitting the wall after 20 miles. There are a number of sports drinks like Gatorade that include supplemental choline, based on this finding. I've never done enough endurance work, myself, to tell whether or not it works.

TB: Was it tested?

RW: It was tested and it does work in the lab. You have to convince the Federal Trade Commission that your claims are substantiated and this requires publications in peer reviewed journals.

TB: During the years you have collaborated with many people. You talked about your work with Julie Axelrod, your wife, and your graduate student, John Fernstrom. You have also mentioned the name of John Growden.

RW: John is professor of neurology at Harvard and directs the Alzheimer's Center. He's been my very close friend and collaborator for decades now, and we have done research together on blocking the synthesis of APP, the source of amyloid, which might be therapeutic in Alzheimer's

disease. We've discovered that the synthesis and metabolism of APP are both controlled by neurotransmitters. We also found that any neurotransmitter that increases the formation of diacylglycerol (DAG), a second messenger, will enhance the formation of soluble APP and block the formation of β -amyloid. That also may be useful in Alzheimer's disease. Then, with Robert Lee in my laboratory, we found that the synthesis of APP is controlled by cyclic AMP, and anything that increases cAMP, like noradrenergic β -receptor activation, will enhance the production of APP, while anything that suppresses the formation of cAMP will have the opposite effect.

TB: So, anti-inflammatory drugs might be useful in the treatment of Alzheimer's disease, and possibly also in the treatment of Downs syndrome.

RW: When this was first suggested by Pat and Edith McGeer, some people laughed. I didn't, I thought it made good sense. The suggestion was based on findings that women with rheumatoid arthritis, who had been taking large doses of aspirin for a long time, or people with leprosy taking dapson, tended to have less Alzheimer's. But, you're quite right that anti-inflammatory drugs might be useful in the treatment of Alzheimer's. The origin of the idea was in epidemiologic studies, as is the origin of so much medical knowledge.

TB: During the years you have been at MIT you trained many people. You already mentioned a couple. Would you like to mention a few more?

RW: It's hard to do this, because those who don't get mentioned may be unhappy, and I love them all!

TB: You have had many publications. How many approximately?

RW: About a thousand publications.

TB: A thousand?

RW: Yes, but I've always had a big laboratory.

TB: How many people are in your laboratory?

RW: Now, the number is down. If you include the clinical people it's down to about 18 or 20 people. But most of the time it's been more like 30 people.

TB: So, it's a large laboratory.

RW: Yes, it's been a large laboratory.

TB: You have also written several books. Could you say something about them?

RW: My first book was on melatonin. It was done with Julie and with an anatomist, Doug Kelly. Another early book I wrote was on catecholamines. Then, I compiled a series of books with my wife on nutrition and the brain. These may have contributed to getting that field started. I have also published a series of books emanating from the Zurich Alzheimer's meetings. What I'm working on right now is not a book, but a summary article which goes back to my origins in philosophy of history. I got interested a few years ago in the question, why is it that when I was a child, in the 40's, 50's, and early 60's, every year some terrible disease that had been untreatable became treatable for the first time. The list of the medications that first appeared during the 40's, 50's, and 60's is extraordinary. And, then, starting around the mid 1960's, even though there was four times the money available, and a vast increase in basic knowledge, this process apparently came to an end. If one makes a list of things that killed people in 1965 and you looked at it again in 1995, it contains more or less the same diseases in the same proportions; the major cancers, congestive heart failure, Alzheimer's disease or lupus, drug addiction, alcoholism. There has been a slowing of progress. What is responsible for this paradoxical relationship between treatment discovery and basic knowledge? I've interviewed many scientists and clinicians and am trying to identify the factors that seem to be most important in enabling the discovery of effective treatments for diseases. And, by the way, effective treatments don't necessarily mean new drugs. We've also seen, over and over again, that off label discoveries, for instance, the discovery that spironolactone, which was used 30 or 40 years ago for treating hyperadrenocorticism, markedly reduces death from heart failure. The same applies to the ACE inhibitors, developed for treating hypertension, which are now shown to reduce death from heart failure. So, I've been interested generically, in what factors determine whether a society is or is not successful in discovering effective new treatments. One major set of factors is resource allocation. One conclusion, which is hardly radical, is that we haven't spent enough on clinical physiology. For decades we've endured starvation of funds for training and supporting the research of clinical investigators. I hasten to add, I'm not talking about myself; I'm fortunate to be well supported. Another factor is the failure sometimes to include the other key disciplines involved in treatment discovery, such as medicinal chemistry, epidemiology, and pharmacology. And, then, a year or two after starting this project, I realized that at least one horrible disease had become treatable, perhaps an exception to the rule.

TB: What is that horrible disease?

RW: It's HIV/AIDS. The natural history of AIDS is so transformed from the way it was five years ago, that it's almost unbelievable. Here was a disease that was almost universally fatal and now, my friends who are AIDS doctors tell me, people who come in with a brand new diagnosis of HIV and can afford treatment are probably not going to die of AIDS. So, I tried to analyze, wherein was that disease different? Why did AIDS become treatable when other diseases didn't? It turned out the limiting factor was not science. The key scientific publication that led to the treatment of AIDS came from a Japanese pharmaceutical company six months after the virus was discovered. So, if fundamental research on HIV had stopped, in 1986, it would have made no difference. The key fact was the discovery that the particular protease which the HIV makes is an aspartyl protease. Since human renin is an aspartyl protease, for a long time drug companies were trying to make aspartyl protease inhibitors for treating hypertension. Eventually, they found that ACE inhibitors were better, so they had large numbers of aspartyl protease inhibitors on their shelves. They knew how to make them. The discovery you have to combine several drugs to treat AIDS wasn't really a discovery. Any doctor who had treated tuberculosis or childhood leukemia, knew that when you're dealing with a rapidly mutating organism, you've got to combine several drugs. What were needed were the drugs. In the latter part of the 1980's, enough political pressure was brought on the FDA to change the way it regulated AIDS drugs. Instead of taking four or five or six years to go through the regulatory process, it now takes four or five or six months, or even less. So the pharmaceutical companies decided now there was the chance of making some money out of AIDS and society would pay for the drugs. So, bang, bang, bang, within a very short period of time, there were ten approved aspartyl protease inhibitors. The point is that a lot of different factors can influence our success in inventing treatments. They can be basic scientific. They can be epidemiologic. They can be clinical. They can be regulatory. They can be political. They can be all kinds of things.

TB: I understood you have a clinical center and patients available for research. How much are you involved in the clinical center and in evaluating patients?

RW: The patients, who come into the CRC, are not there for primary diagnosis or treatment. They're people that satisfy certain inclusion criteria for admission to a study. So, I'm the principal investigator of three programs at the CRC, but a very strong co-investigator runs each of the

studies. My wife runs the studies related to carbohydrates, serotonin, eating, etc., and she has her own staff and her own independence. Another person runs the melatonin studies.

TB: Do you see any of the patients associated with the three programs of which you are the principal investigator?

RW: Now and then, but I don't see them very much. I see and sign all the records. Basically my role is hypothesis and protocol generation, overseeing the protocols are followed, and trying to make some sense of the findings when the studies are completed. But, having this clinical research center is marvelous, because, without it, there's no way I could afford to have nurses, dieticians, and the other people we need in our studies.

TB: Now, one of your major interests is related to eating.

RW: This happens to be the interest of my wife. I married somebody who wanted to make a career out of studying rats.

TB: Rats?

RW: When we were married 40 years ago, my wife wanted to be a teacher; she thought she'd get a Master's in teaching and, then, retire to the suburbs. That lasted about six weeks. Then she went back to school and took a Ph.D. at George Washington University, while I was at the NIH, and finished her thesis at MIT in the biology department. After she finished her Ph.D., with two young children and a very demanding husband, she couldn't embark on a full time career, so she taught at a local college and made exhibits for the Boston Science Museum. Then, around the mid 1970's, I had found that foods affect the brain and decided I needed somebody with knowledge of nutrition to help me develop this field. While she had been teaching biochemistry at a local girls' Catholic college, she was asked, "to teach nutrition." And she said, "I don't know any nutrition and to teach it I'll need to learn some." So, she took a two year post-doc in nutrition, during which she became interested in the area and particularly, in obesity. So, when I discovered I needed a collaborator, I invited her to become that person. She agreed to do so. After we'd been married 15 years, we started to collaborate in the lab. The purpose of our collaboration, initially, was to see whether this ability of serotonin neurons to monitor eating is involved in nutrient selection. We found that it was in rats. We published papers on it, and then, she got interested, and started working for free, in an obesity clinic. It was especially important: she listened to her patients and asked what they were eating. The patients described to her what they ate at mealtime. She also asked them what

they ate between meals, how many potato chips, and how many cookies. So, she came up with this concept of carbohydrate craving. Then we started to work on obesity, because that was where her interest was, and there was something to do.

TB: What about your interest in nutrition?

RW: I entered basic research in nutrition through an MIT colleague, Hamish Munro, as I mentioned.

TB: Is there anything else you would like to add?

RW: I can't imagine.

TB: On this note we should conclude this interview with Dr. Richard Wurtman. Thank you very much, Dick, for sharing this information.

RW: Well, it's been great pleasure.

66. THOMAS A. BAN: interviewed by Leo E. Hollister

LH: It's Monday, December 9, 1996, and we're at the annual meeting of the American College of Neuropsychopharmacology, in San Juan. I am Leo Hollister and today I am going to be interviewing an old hand in this field, Tom Ban.⁶⁸ Tom, welcome to San Juan for the umpteenth time and we have the great pleasure to talk with you. You and Tom Detre, I think, are the ACNP's biggest beneficiaries from Hungary.

TB: Thank you, Leo.

LH: After the uprising or whatever it was, in 1957, you both immigrated and both wound up in the ACNP. Were you a full pledged psychiatrist when you left Hungary, or were you just in medical school?

TB: I graduated from medical school in 1954, and had two years of psychiatry, before I left.

LH: Oh, you'd had some psychiatric training?

TB: Yes. We didn't have a formal residency training program in Hungary, at the time, but I was working as a junior physician at the National Institute for Nervous and Mental Diseases in Budapest.

LH: I see.

TB: I even had my first exposure, in Hungary, to some of the new psychotropic drugs, like chlorpromazine (CPZ), reserpine, etc.

LH: Now, I suppose there were quite a few who left Hungary at that time? They didn't like to live under a communist regime. At least, Hungary is in better shape today than it was then. Now, you came to join Heinz Lehmann in Montreal. Had that been arranged before you arrived to Canada?

TB: No.

⁶⁸ Thomas A Ban was born in Budapest, Hungary in 1929. He was initially trained in psychiatry at the National Institute for Nervous and Mental Diseases in Budapest. When he left Hungary in 1956, he obtained a fellowship at the Montreal Neurological Institute, followed by further psychiatric training at McGill University. During his time at McGill, he conducted research in psychopharmacology and conditioning in psychiatry. In 1976, he moved to Vanderbilt University to direct the clinical division of the Tennessee Neuropsychiatric Institute. He was interviewed in San Juan, Puerto Rico on December 9, 1996.

LH: Well, then, what made you go to Montreal, of all the places in North America that you could have gone?

TB: After I left Hungary, I was working for about two months at the psychiatric clinic of the University of Vienna in the EEG laboratory primarily. I was also involved with some of the patients at the clinic, mainly as an interpreter. While trying to find a place in the world where to go, I wrote to Wilder Penfield, and in my letter I mentioned that as a medical student, I had won an award in a competition with my dissertation on post-traumatic epilepsy. It was a real surprise that he answered and an even greater surprise that he generously offered a fellowship in his Institute.

LH: Penfield was a giant. The Montreal Neurological Institute at that time was world class.

TB: It was a fantastic place.

LH: So, that's how you got to Montreal and then, it was just sort of accidental that you got to work with Heinz Lehmann?

TB: It was not completely accidental. After my arrival to Canada, in January 1957, I spent six months at the Montreal Neurological Institute (MNI). My assignment was in neuroanatomy but I also participated in the activities of Herbert Jasper's neurophysiology division and attended the epilepsy and multiple sclerosis clinics.

LH: Did you have any contact with Penfield?

TB: I had some contact with Penfield, but it was Francis McNaughton who took me under his wings. Then, I did a rotating internship at the Victoria General Hospital of Dalhousie University, in Halifax. I spent two months from that year at St. Joseph's Hospital, in Glace Bay, Cape Breton Island delivering babies, before returning to Montreal.

LH: How did this happen?

TB: During my internship, I applied to the residency-training program in psychiatry at McGill.

LH: So that is how you got to work with Heinz.

TB: Yes. I marked on the applications form that my preferential first rotation would be the Verdun Protestant Hospital, one of their training facilities, because I knew that Dr. Lehmann was the clinical director of that hospital. I didn't know him, but I had read one of his papers, while still in Hungary, and heard people talking about him, while I was at the MNI and also at Dalhousie. I became interested in psychopharmacology very soon after I started at the National

Institute.

LH: By using chlorpromazine?

TB: After using chlorpromazine for a couple of months in a limited number of patients, I became so enthusiastic about its advantages over the old treatments that I persuaded Dr. Sandor, our service chief, that we start in the Institute a quarterly publication on new developments in neuropsychiatry, and especially, in pharmacological treatment. So, I was familiar with Lehmann's name already in Hungary from reviewing the literature for our publication.

LH: Sure. Well, you made a lucky contact. Actually, you got a mentor right at the top. TB: Yes, I was very lucky. I met Dr. Lehmann for the first time at the Verdun Protestant Hospital, on the 1st of July 1958. It was the first day of my residency.

LH: I guess, by that time, Heinz was pretty heavily into research, wasn't he?

TB: Yes, he was. He already got his Lasker award for his contributions to the clinical development of CPZ, about a year before that. And, I think he had just published his paper, the first paper in North America on imipramine.

LH: I think so.

TB: Heinz was very much involved in psychopharmacology and in all kinds of other research in psychiatry in those days, and within a month, I was working with him on several of his projects. In fact, I started to work with him on the second day of my residency. He was interested in the effects of drugs on biological systems of low complexity, at the time, and we were studying the effects of prototype drugs like dextroamphetamine, secobarbital, chlorpromazine, prochlorperazine, imipramine, lysergic acid on enzymological, growth, and reactivity systems. I worked with urease, firefly lantern extracts, proteus bacteria, oat seedlings, the feeding reflex of hydra, and dandelion sleep movements. We were also trying to make mute patients speak by inducing fever, giving ECT, and administering them amobarbital, dextroamphetamine, chlorpromazine, LSD, etc.

LH: Now, how long were you in Montreal?

TB: About nineteen years.

LH: Nineteen years. Of course, during that time, you become more and more an independent investigator.

TB: Yes, but all those years, Heinz and I worked very closely together. The first independent line of research I conducted was in conditioning. It was supported from a grant I received from the Medical Research Council of Canada. But, actually, I got involved even in that area of research on Heinz's initiative. At the time, to get our diploma in psychiatry at McGill, we had to write a thesis and I got involved in research in conditioning because the hospital had a conditioning laboratory and Jim Prescott, the psychologist who set up that laboratory was leaving.

LH: So, it was the laboratory that dictated your career.

TB: Yes and essentially that Heinz was looking for someone who might be interested to do research with him in the conditioning laboratory.

LH: He had done a lot of such work before he got into chlorpromazine.

TB: That's right. He had done a lot of research with psychometric performance tests, and also, some research in psychophysiology. For my thesis, I had to review the literature on classical conditioning and had to do also some laboratory research in conditioning in human.

LH: When did you finish your training?

TB: I received my diploma in psychiatry from McGill, in 1960. My thesis, *Conditioning and Psychiatry*, was published with some minor modifications as a monograph, first in 1964, by Aldine in Chicago, then in 1966, by Unwin in London. The foreword to the book was written by Horsley Gantt, at the time one of the last living disciples of Pavlov. During the 1960s, my research in conditioning and in psychopharmacology was closely linked.

LH: So, this is how you got involved in conditioning research.

TB: My objective was to develop a common language for mental pathology and psychotropic drug action, using conditioned reflex variables. To bridge the gap between pharmacodynamics and psychopathology, we developed a conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects. I perceived conditioned reflex variables as functioning patterns of the central nervous system and described mental pathology and the action of psychotropic drugs in terms of the presence or absence of these variables, such as the startle response, extinction of the orienting reflex, acquisition and extinction of the conditional reflex, delayed and trace reflex formation, and so on. One of our papers on the development and use of the battery won the Canadian Psychiatric Association's McNeil Award in 1969.

LH: So, your first line of inquiry was in classical conditioning.

TB: Yes, but I combined some of our research in conditioning and psychopharmacology. We had some interesting findings in those studies.

LH: For example?

TB: For example, findings in one of our studies indicated that changes in orienting reflex behavior was more closely linked to a favorable response to neuroleptics in schizophrenia than the appearance of fine tremor in the hands.

LH: Well, I know you've been one of the few people in our world, who has tried to develop new tests based on classical conditioning for identifying biologically homogenous diagnostic populations in psychiatry. Are you very happy with the present state of affairs in psychiatric diagnosis?

TB: Well, I think, at least in the past 15 years or so, we are trying to develop a common language for diagnosing patients. LH: At least, we are defining our terms.

TB: We have at least diagnostic categories that can be reliably identified. Consensus-based diagnoses undoubtedly are an important step forward in the provision of psychiatric services. They might also be useful in epidemiological research. The problem is that they are detrimental for progress in nosological research. They cover up their component diagnoses that might be selectively affected by psychotropic drugs. It seems the use of consensus-based diagnosis has not provided the necessary feedback for developing clinically more selective and thereby more effective psychotropic drugs.

LH: Well, I think it is a step forward to have this common language and that we all have definitions for diagnoses, but I sometimes wonder whether it might not get in our way because it lumps all kinds of people together and labeled, for example, as schizophrenic.

TB: The diagnostic concept of dementia praecox, or schizophrenia, as you know, was created by Kraepelin by pooling together three major diagnostic categories of illness, hebephrenia, catatonia, and dementia paranoides on the basis of their course and outcome. From the time of its inception, the diagnostic concept of schizophrenia has been challenged. Karl Kleist, in the 1920s, divided schizophrenia into two classes of disease, and his disciple Karl Leonhard divided it into two classes with three forms and several sub-forms in each. In the 1980s, I had a grant from NIMH at Vanderbilt, to study chronic schizophrenia. And in this study, we showed that each form and sub-form of the two classes of disease Leonhard described, exist. In fact, there were no major changes

in the distribution of the different forms and sub-forms of disease in Christian Astrup's patient cohort, in the 1950s, in Oslo, from Leonhard's patient cohort, in the 1930s, in Berlin, and in our patient cohort, in the 1980s, in Nashville.

LH: That's telling evidence that there must be something real about them. How about the stability of the diagnoses?

TB: We developed two diagnostic instruments and with both we could reliably identify each form and sub-form of disease in Leonhard's classification, but we didn't study the stability of the diagnoses. Clinically, patients who are diagnosed with one or another of the sub-forms of the continuous forms of the disease, referred to as systematic schizophrenias, seem to display constantly the same syndrome, whereas patients diagnosed with one or another sub-form of the episodic forms of the disease, referred to as unsystematic or non-systematic schizophrenias, are more difficult to diagnose when in partial remission. But in relapse, they seem to display the same syndrome as in their prior episodes. The same applies to unipolar depression, a class of disease in Leonhard classification that is also divided into two categories of disease, pure melancholia and pure depression. These are episodic diseases and arguably patients are symptom free, between episodes. But it seems that in repeated episodes, patients are diagnosed with the same subform.

LH: Well, that's true in individuals. Well, how about the concept of spectrum disorders, like depressive spectrum or schizophrenia spectrum diseases?

TB: The concept of spectrum disease implies a relationship between diseases. It is a broadening of a pharmacologically and genetically already broad, heterogeneous category of disease. We need narrower, biologically more homogenous populations for neuropsychopharmacological research.

LH: What do you think about diagnoses like dysthymia? They surely are depressed but they don't meet the criteria of a full-blown major depression. Does that make any sense to you to have these kinds of diagnoses?

TB: Patients diagnosed with dysthymia have depressive personalities displayed by all kinds of depressive symptoms. They don't have a depressive disease, in which the mood transforms their experiences.

LH: Let me ask you a question. How much of what we see in these diseases is organic, biological, and how much is functional, the result of interaction with the environment?

TB: In spite of my research in conditioning and my interest in learning theory, I look at the different forms and sub-forms of schizophrenia as natural forms of disease, in which the interaction with environment plays little role. But, then if you look at the disorders in the DSMIV, many of those disorders are probably the result of an interaction between nature and nurture.

LH: Well, I think everybody will agree that it's not just all in our genes. Let me throw another curve at you. How about this issue of co-morbidity? Not only do we have a problem with spectrums, but, we now have an increasing problem of co-morbidity. When you speak of depression, you are often speaking of two or three other things, as well, aren't you?

TB: If you want to get a psychotropic drug prescribed to the widest possible population in which patients have a better chance to respond than to an inactive placebo, the concept of comorbidity is very useful. For neuropsychopharmacological research, in which progress depends on the identification of treatment responsive forms of illness both concepts are counterproductive.

LH: Since we are talking about psychopharmacology and diagnosis, what do you think of Don Klein's idea that you can establish new entities based on the reaction of patients to a particular drug or drugs.

TB: Well, obviously, a diagnostic system based on responsiveness to drugs is desirable. A good starting point would be the identification of treatment responsive forms of illness within the currently used diagnoses. Research in this area must be based on an understanding that responsiveness to the same drug depends to a great extent on the underlying condition.

LH: Your career then in Montreal was in neurophysiology and drugs?

TB: I would say I was primarily doing research in psychopharmacology and conditioning in this order. My primary job was directing the activities of our Early Clinical Drug Evaluation program, as Dr. Lehmann's co-principal investigator of a grant from the NIMH.

LH: That's right. You were part of the ECDEU network.

TB: Yes, we were one of the first grantees and we were there from the very beginning. After the completion of my thesis, I had a research grant as I mentioned before, from the Medical Research Council of Canada to pursue my research in conditioning. But, most of my research in conditioning was closely linked to my research in psychopharmacology.

LH: I see. So, your primary activity was directing the ECDEU.

TB: I spent part of my time, for a few years, on Ewen Cameron's team, who was the chairman of the department, in the late 1950s and early '60s. I was responsible for recording psychophysiological measures after the administration of psychotomimetics, like LSD or psilocybin to our patients. Actually, I got on Cameron's team because he needed someone with some experience in conditioning and with psychotomimetics. My first research project in psychopharmacology, and this was back in 1958, was with phencyclidine, a substance originally developed for general anesthesia, that turned out to be a psychotomimetic.

LH: So, you worked with Heinz Lehmann and also with Ewen Cameron, while at McGill. Did you work with anyone else while there?

TB: I also worked with V.A. Kral in a NIMH funded psychogeriatric program, in which we studied the effects of psychotropic drugs in the aged.

LH: Now, in your work with the ECDEU, I suppose you looked at the same drugs as the others in the network.

TB: I think we worked with all the psychotropic drugs, which were available for clinical investigations during the 1960s and early '70s, in Canada and the United States. Bill Guy, who at the time was with the Biometric Laboratory at George Washington University, told me that they processed more studies from our unit than from several of the other units together. We were among the first in North America to study several of the thioxanthene and butyrophenone preparations. And, with drugs that showed clinical promise, we conducted a series of investigations. We also discussed the findings of these studies at symposia organized by the Quebec Psychopharmacological Research Association. We were especially interested in the differential therapeutic profile of drugs. So in one of our studies, we compared chlorpromazine, chlorprothixene, and haloperidol in the treatment of acute schizophrenia.

LH: That's an interesting comparison. In the company brochure, chlorprothixene was supposed to be good for everything, but it turned out not to be good for very much.

TB: In our study it was comparable to chlorpromazine in acute schizophrenia.

LH: Well, I don't doubt that chlorprothixene was an active drug, but it never went anywhere, you know, never caught on.

TB: We also worked with drugs that didn't catch on in the United States. One of them was methotrimeprazine, Nozinan, and another one was prochlorperazine, Stemetil. They were marketed as antipsychotics in Canada but not in the USA.

LH: I think that decision, though, was probably commercial. At the time, SKF had trifluoperazine and they didn't want another piperazine-phenothiazine to compete with it. So, they developed prochlorperazine as an antiemetic rather than as an antipsychotic, but it's a perfectly good antipsychotic.

TB: Then, we also worked with drugs like trimipramine that was marketed in Canada, in the early 1960s, and in the United States, in the late 1970s.

LH: I think the drug that most of us ignored or didn't pay much attention to at the time, which ultimately, became very important, was lithium.

TB: Yes. It happened that I used it first in Hungary, in 1955 or '56, at the National Institute and I remember we had to get lithium prepared by the pharmacist of the Institute.

LH: The pharmacist had to make it?

TB: Yes. It was not available commercially. We had a couple of patients on it.

LH: It's surprising that you were able to work with lithium so early in Hungary when lithium was discovered in an English speaking country. You would have thought that it would have more impact in Britain or the U.S. rather than it had in Hungary?

TB: Dr. Sandor, my service chief and mentor, was fluent in many languages and he probably read the papers of Schou or Trautner. And he was interested in trying in his patients everything he learned about. We even managed to monitor blood levels. We tried every possible new treatment he ever read about and we were able to put our hands on.

LH: Those were the good old days when you didn't have to go through six committees and have a waiting time of eight months before you could do a study.

TB: We actually did not conduct clinical studies with any drug; we just used them on the ward, trying to help patients. I started to work at the Institute just a few months before chlorpromazine became available. So, I'm probably one of the few survivors who saw how things were before the introduction of the new psychotropic drugs. We didn't have chlorpromazine readily accessible for several months, even after we saw how well it worked. We used it first only in some privileged patients, who were able to get it sent by their relatives living outside the Iron Curtain. I remember

using Largactil from France in one patient, Megaphen from Switzerland in another, and Hibernol from Sweden in a third. I also remember the first patient I treated with chlorpromazine. He was an involuntional melancholic. He was agitated, depressed, delusional, and theatrical as most patients with involuntional melancholia were in the old days, when admitted to hospital. Our plan was to treat him with ECT, when his family got Largactil from one of their relatives in France. He responded promptly to the drug. We were impressed.

My second patient was a negativistic catatonic schizophrenic whom I had to tube feed and catheterize daily for several months. It was a kind of miracle to see him revived, walking and talking and taking care of himself. In both of these patients, we used very small doses compared with current standards, about 25 mg intramuscularly three or four times a day. We knew that we must be prepared for blood pressure drop, orthostatic hypotension. So, after the injection I stayed with these patients and took their blood pressure, every half an hour or so.

LH: In our original studies, we also gave relatively small doses. I am curious what would happen if we would go back to those small doses.

TB: It would be interesting to see. I also had some experience on Dr. Sandor's service with reserpine in schizophrenics and with Hydergine in elderly patients with memory problems. Both these drugs were available in Hungary for clinical use in hypertension in those days. Reserpine was also frequently prescribed as Serpasil for neurotic patients, probably most often for patients with neurotic depression.

LH: Well, I think the whole history of the early development of psychopharmacology has been full with serendipity. Somebody would make a clinical observation that a substance is good for a particular condition and this was sufficient to try to use it in others with the same or similar conditions.

TB: I agree that serendipity played a major role in the discovery of most of our psychotropic drugs, but after a few month of the publication of my *Psychopharmacology*, in which I attributed the discovery of chlorpromazine to serendipity, I received from Henri Laborit a copy of a book he just published at the time, with a dozen or so drugs listed on the blank page of the book in the front with the question below: "All these by serendipity?"

LH: Well, you had nineteen pretty good years in Montreal. Why did you leave?

TB: I accomplished the task of organizing a division of psychopharmacology. It was the first division of psychopharmacology in any psychiatry department in the world. But then, I ran into difficulties in implementing a structural reorganization of the psychiatric service in our hospital in a manner that would use optimally what psychopharmacology could offer. I was also interested in extending the scope of my activities

LH: Was Cameron the chairman of the department all through your stay?

TB: No. Cameron resigned, in 1966.

LH: And, then who succeeded?

TB: Bob Cleghorn. It was during his tenure that I was appointed director of the Division of Psychopharmacology. It was also during his tenure that we became the Canadian National Reference Center for Psychotropic Drugs, part of an International Reference Center Network organized by the Division of Mental Health of the World Health Organization, in collaboration with the Psychopharmacology Division of the National Institute of Mental Health of the U.S.A. Then, in 1970, the activities of our Reference Center were extended to education, and we became W.H.O.'s first training center for teachers in psychopharmacology and biological psychiatry in developing countries. We introduced our fellows into the methodology of clinical investigations. During their six to 12 months stay, they became familiar with the assessment instruments and rating scales included in Bill Guy's ECDEU Assessment Manual. Most of them participated in at least one of our clinical trials, in which the collected data were sent to the Biometric Laboratory Information Processing System that was set up at George Washington University to analyze the data of ECDEU investigators. It was during this period that I began with the translation and adaptation of the AMDP and AGP manuals, used in the documentation of changes in treatment in adult and geropsychiatric patients in German speaking countries. In the mid 1970s, Heinz Lehmann succeeded Bob Cleghorn as chairman of the department of psychiatry at McGill. During his tenure, the activities of the division were extended to all six hospitals affiliated with the Department. In 1976, at age 65, Heinz retired from the chairmanship. And, in the same year, I accepted an offer from Vanderbilt, and moved from Montreal to Nashville.

LH: So, you went to Vanderbilt?

TB: I went to Vanderbilt.

LH: Vanderbilt has always been very strong in clinical pharmacology.

TB: Yes. Now, clinical pharmacology was a division of internal medicine at Vanderbilt that was directed by John Oates. We did our research in clinical psychopharmacology at the Tennessee Neuropsychiatric Institute, part of the department of psychiatry, located on the premises of Central State Hospital. T.N.I. was established from a center grant of NIMH and supported by the Department of Psychiatry and the Division of Mental Health of the State of Tennessee. The late Earl Usdin, Dan Efron, and Morrie Lipton played a major role in getting the center grant for establishing the T.N.I.

LH: Now, who was the chairman of the Department of Psychiatry when you went to Vanderbilt?

TB: Marc Hollender.

LH: He was rather supportive of psychopharmacology, wasn't he?

TB: He was very supportive of my activities but I don't know how supportive he was of my predecessor. Marc was a psychoanalyst, a very well organized, honest man, dedicated to teaching. After my arrival, he referred to me for consultation some of his long-term patients in analytic psychotherapy and we became friends after one of his patients with a phobic-anxiety depersonalization syndrome promptly responded to phenelzine, a monoamine oxidase inhibitor he prescribed on my recommendation. A few months later, when the patient developed delayed and retrograde ejaculation we wrote it up and published it. A couple of years after my arrival, the director of the outpatient clinic died. It took about a year to find a replacement and during this time I spent three half days a week at the clinic supervising residents, and answering their questions related to the use of psychotropic drugs. The questions the residents asked and my answers to their questions were recorded, and Marc decided to edit and organize the material in a logical sequence. Then we complemented the material by a few additional questions and answers. It became a book with the title of *Psychopharmacology in Everyday Practice*, published by Karger, in 1980. Marc and I were very pleased when we learned that our book was translated from the original English into Japanese and Dutch.

LH: I think that having you two on the same book was quite an achievement.

TB: And he really worked on that book. He kept on editing my answers until they were crystal clear.

LH: So, it wasn't primarily a tag along authorship.

TB: It would have been a very different book if he had not done his part.

LH: What do you think of writing books? I always thought you make more money digging ditches.

TB: You are probably right, but I never looked at it like that.

LH: Well, it's not only the money; that's probably the least of it. It's the fact that you hope it will have some influence, but even then, you're always dubious about it.

TB: Writing a book forces me to conceptualize the findings in our research and integrate it with the information in the literature. And, that, in itself, I find a rewarding experience. Now, I should add that it takes me a long time to write a book or a review because I keep on conceptualizing and re-conceptualizing my findings until I find the way to express what I would like and be able to communicate it.

LH: That's one of the beauties of writing a book. You can philosophize, or tell anecdotes, or things that are more personal. And, I find it rather discouraging that many of the new books are lacking this personal touch. All you've got is a lot of information. It does not make any sense to write a book if the author's personal touch is not there.

TB: I think not only books, but also reviews should have the identity, the conceptualization of the reviewer. A good review should be more than a summary of all the papers.

LH: Now, when you went to Vanderbilt there was the beginning of a budding institute there, wasn't there?

TB: The Institute, the Tennessee Neuropsychiatric Institute was founded about ten years before my arrival.

LH: That was when Fridolin Sulser went there?

TB: Yes, Fridolin went there about that time. I think he got to the Institute just a little bit after Jim Dingell.

LH: Now, didn't John Davis spend some time there?

TB: That's correct. John Davis was the first clinical director of T.N.I. But I think John Davis and Dave Janowsky, his close associate, arrived considerably later than Dingell and Sulser. And, when John left for Chicago, Dave Janowsky, Eddy Fann, and other members of John's team left, as well. There was no one there on the clinical side for two or three years before I came.

LH: Did you take John Davis' place?

TB: Yes, I was John's successor. But there was a period of time between John's departure and my arrival, during which all the funds of the Institute were used by the preclinical division. The

Institute also had a Center grant, which just expired around the time of my arrival. At the time John arrived, the Institute was prosperous, whereas at the time of my arrival, virtually all the money the Institute had was used by the pre-clinical division. There was not enough money there to operate a clinical research service safely.

LH: So, you came there when they ran out of money.

TB: The Center grant expired and it was up for renewal. To be able to present an acceptable research grant proposal I had to organize a clinical unit first.

LH: Could you transfer your ECDEU grant there?

TB: Our ECDEU grant with Dr Lehmann was terminated a few years before I left McGill. In fact, just about the time I moved to Nashville, ECDEU's Biometric Laboratory was closed, and some of the professional staff of the Laboratory, Bill Guy and David Schaffer joined me at Vanderbilt.

LH: Did the funding for the continuous operation of TNI come from the state or private sources?

TB: It came from three sources: the State of Tennessee, Vanderbilt University, and the National Institute of Mental Health.

LH: You were at Vanderbilt when Earl Sutherland was there, weren't you?

TB: He died before I arrived.

LH: So, you never had a chance to know him.

TB: No, I just knew that he got the Nobel Prize.

LH: Now, what was your primary thrust at Vanderbilt in psychopharmacology? Were you continuing to test new drugs?

TB: I continued with clinical investigations and we tested several new drugs but the primary thrust of my research was in developing a methodology that would identify the treatment responsive forms of illness, or sub-populations within the diagnostic categories, to psychotropic drugs. Development of a pharmacologically valid psychiatric nosology was central to my research during the past 40 years. Since pharmacokinetic factors did not seem to explain why one patient in the same diagnostic category responds, whereas the other remains refractory to the same psychotropic drug given in the same dose. As early as in 1969, in the concluding remarks of my *Psychopharmacology* I noted that the "introduction of therapeutically effective psychotropic drugs focused attention on the pharmacological heterogeneity within the diagnostic categories of mental illness." For some time, I believed that biological measures would identify pharmacologically

homogenous groups within the diagnostic categories of mental illness, but by the mid 1980s, it became evident to me that this was not the case and that biological measures were state dependent epiphenomena of mental illness. I published a paper on this with the title, “Prolegomenon to the Clinical Prerequisite: Psychopharmacology and the Classification of Mental Illness.”

LH: It’s in an interesting title.

TB: The paper was an extension of my presentation on “Psychopharmacology and the Classification of Mental Illness” at a symposium at the 15th CINP Congress that was held in San Juan, in 1986, in the same hotel we are now. After my presentation, I went to the beach with Corneille Radouco-Thomas, who was at the time the editor-in-chief of *Progress in Neuropsychopharmacology and Biological Psychiatry*, and in the course of our conversation he told me that he would be interested to publish my presentation in his journal. He even suggested “Prolegomenon to the Clinical Prerequisite” as a possible title. I thought it was a good suggestion and the paper was published in his journal, in 1987. In Prolegomenon, I argue that it’s not only unrealistic to expect that biological measures would provide pharmacologically meaningful clinical categories of mental illness in the foreseeable future, but I argue also that we need clinical end-points to render findings with biological measures clinically interpretable.

LH: Now, as someone who has been interested in methodology of studying drugs, are you happy with the way things are today? You know that most of the companies now have in-house help that is able to develop a protocol and also have the statistical help to analyze the results. They usually vend out the writing of the paper to some professional writing group and all the investigators do today is gather data. It seems to me like a very dull way to do business.

TB: This is correct and very unfortunate. But I wouldn’t blame the companies for doing that. They are business organizations responsible to their shareholders to generate maximum profit. It is the task of the profession that the new psychotropic drugs are optimally used in individual patients. To meet regulatory requirements, companies must demonstrate that their drug is not toxic and is efficacious in treatment in at least one of the consensus-based diagnostic groups of mental illness. By the accepted standards, a drug is proven efficacious if it is statistically significantly superior to placebo in two clinical studies in that population. We have been aware for some time that our consensus-based diagnoses are pharmacologically heterogeneous, so, it would have been the task of academic psychiatry to extend clinical drug development with clinical psychopharmacological

research to identify the treatment responsive subpopulation to psychotropic drugs. I have been rather frustrated for some time that this is not done at the universities, and I just formed a small company with some of my former associates and a few other interested psychiatrists to fill in this gap in clinical drug development. It was just formed. I retired from my professorship from Vanderbilt to be able to dedicate my time in developing the company.

LH: What's the thrust of the new company?

TB: The development of psychotropic drugs in a manner that they can be used selectively. We intended to achieve our objective by developing a methodology for the identification of treatment responsive forms of illness, employ the new methodology in multi-center clinical investigations, and delineate the differential therapeutic profile and indications of psychotropic drugs. We hoped to be able to generate the necessary support from industry, government, and foundations to achieve our objectives.

LH: Do you think our clinical tools are sensitive enough to pick up minor differences in the pharmacological profile of psychotropic drugs.

TB: I don't think that the current methodology of clinical investigations with behavioral rating scales focused on the detection and demonstration of efficacy has the necessary sensitivity. But there are some findings that indicate that the Diagnostic Criteria of Research Budapest-Nashville, we developed at Vanderbilt in collaboration with Bertalan Petho's group at Semmelweis University, has the necessary sensitivity. The DCR is based in part on Leonhard's classification of endogenous psychoses. As you might know, some 40 years ago, Frank Fish had shown that one subpopulation of unsystematic schizophrenia in that classification, affect-laden paraphrenia, responds selectively to phenothiazine neuroleptics. There are also some indications that the Composite Diagnostic Evaluation or CODE System provides the necessary sensitivity for the detection of differences in the pharmacology of psychotropic drugs.

LH: That's an interesting and ambitious undertaking. Let me go on to another facet of your multi-faceted career. I remember I recently picked up a copy of *Thirty years of CINP*, a book you and Hanns Hippus edited some years back. More recently, of course, I've been going through your *History of the CINP* that you and Oakley edited together. You've been interested in history for a long while, haven't you?

TB: All through my professional career I have been interested in the conceptual development of disciplines like psychiatry and neuropsychopharmacology. I also enjoy figuring out or reviewing developments that lead to our current state of affairs. It is difficult for me to see how research could contribute to the development of a field if it is not done in a historical context.

LH: It would help to have the historical context to put things in. I'm generating a letter, currently, to the *Journal of Psychiatry* because they had a letter saying neuroleptic drugs are unpleasant to take. I thought that was common knowledge thirty years ago. And, the problem, it seems to me, is that the indexing systems that are now searching the literature so easily and completely, go back only about fifteen years. And, it's like there's no history beyond fifteen years ago.

TB: It is very disappointing that we have the capability to review historical development properly with the help of computers and we don't use this capability fully.

LH: Now, you and Oakley, are undertaking a similar task with the ACNP history, is that right?

TB: This is, more or less, the case. It would be more correct to say that we are ready to undertake the task.

LH: Well, I think these kinds of interviews are very good, historically, but I'm still a print man. This project, with all the visuals, is important but I still would like to see something written in print.

TB: I'm very glad to hear that because we would like to see these interviews transcribed and in print as well.

LH: You know, David Healy has been doing something similar to what you are doing, but actually, he is writing up these interviews rather than filming them. And, I found the first volume of his interviews very interesting. But, there are of course several different approaches to presenting a coherent historical account.

TB: We seem to have the necessary information in these interviews to present in print a coherent account on the history of the field. Do you think it would be a worthwhile undertaking?

LH: I think it's a worthwhile undertaking, yes.

TB: We are ready to do it. That's all I can say.

LH: You see the problem is that many organizations start off with no concept that they are going to want, someday, to know what their history was, and so they ignore it for the first decade or two. And then, all of a sudden, someone says, "Gee whiz, we've got a history!"

TB: As you know, we have already put in print the history of the CINP. I think it will be much easier to reconstruct the history of the ACNP because ACNP's record keeping has been much tidier from the beginning. And I have a feeling that probably in the "Oakley era" that began with his election as Secretary/Treasurer, in 1979, we will be able to find all the records we need.

LH: You know, there's a depository of information that they're setting up with Vanderbilt now. It's fine, but really I don't have any old notes. I, periodically, cleaned out my files and pitched them. I guess some people are compulsive about keeping things.

TB: I think it is very fortunate that finally we have an archive. It was Oakley who got the necessary funds to start it.

LH: Well, Tom, you've not only been a historical figure but now you're a major historian of both of the large organizations connected with the world of psychopharmacology. And, I certainly wish you well in your venture to put it in a coherent, logical, and written form. I think a lot of what comes out of these interviews are personal things, the people you've met along the way and people who have influenced you and so on.

TB: I remember, Leo, when we first met.

LH: You do?

TB: Yes, I do.

LH: Your memory is better than mine. I've got a few years on you though.

TB: You were already well known in the field. It was, in 1960 or '61, at the first ECDEU investigators meeting in Washington D.C. At the time, the group was small; we could still sit around a table.

LH: Well, one of the great things, from my point of view, of being in this field has been the wonderful people, the bright people that you meet along the way, some of whom become very good friends and others you cherish and who follow you. And, I think we live in a wonderful era and we're lucky to be in the field we're in.

TB: Yes, we are very lucky.

LH: Well, there's been a great deal of progress since you and I began and I hope we will be able to see some of the bright future that seems to be in the making.

TB: I hope so.

LH: OK, Tom.

TB: Thank you, Leo.

67. THOMAS A. BAN: Interviewed by William E. Bunney, Jr.

I'm William Bunney and I'm interviewing Dr. Thomas Ban⁶⁹. It is December 10, 2007. We are at the annual meeting of ACNP in Boca Raton. Tom, could you begin by telling us something about your background, early interests, and how did you get started in medicine?

TB: I was born, in 1929, in Budapest, Hungary in a middle class family. As far as I can remember, I was interested in books and in my teens I was a voracious reader, wrote poems, short stories, and even a book. At age sixteen, I won a student competition award for an essay on the transformation of the 18th century novel in the early 20th century; I attributed it to the influence of Freud and psychoanalysis. I was encouraged to prepare for a career in literature. But, my world that had collapsed with World War II was changing again. Hungary became a

“people’s democracy,” and I thought it would be safer to enter medical school. WB:

What about college?

TB: We went straight to university from high school, but I had the equivalent of a college education by auditing courses in history and philosophy.

WB: Where did you go to university?

TB: The Medical School in Budapest, in 1948. It was the old Semmelweis Medical University, only the name had changed.

WB: When did you get your medical degree?

TB: In 1954.

WB: Did you do any research during the time you were in medical school?

TB: No, but in the fourth year, with a classmate of mine, we received First Prize for our essay on *Post-traumatic epilepsy*. It was also during that year I became interested in psychiatry. I was fascinated by the lectures of Gyula Nyiro, our professor. He was a structural psychopathologist who viewed mental symptoms as abnormalities in the processing of signals between and across

⁶⁹ Thomas A Ban was born in Budapest, Hungary, in 1929. He was initially trained in psychiatry at the National Institute for Nervous and Mental Diseases in Budapest. When he left Hungary in 1956, he obtained a fellowship at the Montreal Neurological Institute, followed by further psychiatric training at McGill University. During his time at McGill, he conducted research in psychopharmacology and conditioning in psychiatry. In 1976, he moved to Vanderbilt University to direct the clinical division of the Tennessee Neuropsychiatric Institute. He was interviewed in Boca Raton, Florida on December 10, 2007.

different levels of three mental structures corresponding with the three neuronal component of the reflex.

WB: When you got out of medical school, what did you do?

TB: I got a job as a junior physician at the National Institute of Nervous and Mental Diseases.

WB: What about residency?

TB: We did not have residency training. I started on one of the services of the Institute where patients with “neuroses,” called anxiety disorders today, were treated.

WB: How were they treated?

TB: Most of them were given tonics, like Arsotonin and Strychnotonin by daily subcutaneous injection. We did psychotherapy, quite frequently with chemically-induced abreactions, and hypnosis in some patients.

WB: How long were you on that service?

TB: For six months. Then, I was assigned to one of the admission services at the Institute.

WB: What kind of treatments did you have there?

TB: We had a morphine-scopolamine combination for controlling agitated and violent patients, and a phenobarbital and bromide combination, BromSevenal, for sedation. We also used paraldehyde and chloral hydrate. We treated schizophrenia with insulin coma, depression with tincture of opiate, and both with ECT. Then, sometime in the spring of 1955, we had our first patients on chlorpromazine and reserpine. We also had a couple of patients on lithium.

WB: You used lithium in the mid-1950s?

TB: Yes, in 1955. György Sándor, my service chief followed the literature very closely. I remember having our lithium supply prepared in the pharmacy and the Institute had a flame photometer to monitor plasma levels.

WB: Did he publish?

TB: Dr. Sándor was not interested in writing papers, but, to my surprise, he was open to my suggestion, when the new drugs appeared, to start a quarterly Digest for the Institute to keep everyone abreast of developments.

WB: Did you publish any papers in Hungary?

TB: I published three brief reviews. One was on the development of the diagnostic concept of neurosis, another on the story of “BromSevenal,” and the third was an overview of the history of psychiatric nursing.

WB: It seems that you got your first experience with the new drugs in Hungary?

TB: I had my first exposure to some of the new drugs.

WB: Did you use Marsilid (iproniazid) in Hungary?

TB: Marsilid was used only at our special service for tubercular patients.

WB: Was it used in depression?

TB: No, it was only used in the treatment of tuberculosis.

WB: When did you leave Hungary?

TB: In November 1956, after the revolution.

WB: You went to Montreal?

TB: Before Montreal, I spent a few weeks in Vienna at the University Clinic of Hans Hoff. I started with my fellowship at the Montreal Neurological Institute (MNI), in early January 1957.

WB: How did you get that fellowship?

TB: I wrote to Wilder Penfield and told him about my essay on post-traumatic epilepsy. I also told him that I would like to further my my traing in his Institute. I was familiar with the monograph he wrote with Herbert Jasper on “Temporal Lobe Epilepsy” and the “Functional Anatomy of the Brain” from editing our Digest. I did not expect he would respond, but he did, and even contacted the Canadian authorities to issue me an immigrant visa. In less than two months after I crossed the Hungarian-Austrian border, I was attending Francis McNaughton’s epilepsy clinics, and Herbert Jasper’s research rounds at the MNI. In June 1957, I left for Halifax to do a rotating internship at the Victoria General Hospital of Dalhousie University. A year later, I passed the Canadian Medical Council examinations, which allowed me to apply for a license to practice medicine.

WB: How did you get to work with Dr. Lehmann?

TB: I was accepted in McGill’s residency training program and was assigned for my first year to the Verdun Protestant Hospital (VPH), a large psychiatric hospital affiliated with McGill that served the English speaking population of the city, where Dr. Lehmann was clinical director. I met Dr. Lehmann for the first time on the 1st of July 1958, and, a few days later, I started to work with him on some of his research projects.

WB: How did this happen?

TB: Doctor Lehmann asked whether any of us new residents would be interested to work with him on some of his projects.

WB: How many of you were interested?

TB: From the six of us, only me. But later on, some of the others got on board.

WB: What was your first project?

TB: I got involved with several projects simultaneously. In one, my task was simply to stay with some of my fellow residents and other psychiatrists who were given psilocybin.

WB: Psilocybin?

TB: At that time it was thought educational for those dealing with psychotic patients to get an idea about what patients were experiencing.

WB: What about the other projects?

TB: In another project, we studied the effects of prototype CNS acting drugs, like dextroamphetamine, secobarbital, chlorpromazine, prochlorperazine, imipramine, and lysergic acid on enzyme functions and on biological systems of low complexity, including urease, firefly lantern extracts, proteus bacteria, oat seedlings, the feeding reflex of hydra, and dandelion sleep movements. And, in a third, we studied the effects of phencyclidine (Sernyl), in different doses and in different diagnoses, as well as in a few normal subjects. Dr. Lehmann received a supply of Sernyl from Parke Davis to find out whether it would be suitable for the facilitation of psychotherapy. It was not, but I became interested in the compound and it did not take me long to recognize it was a substance that could change how one experienced oneself and the world. Its effects were distinctly different from psilocybin. Just from curiosity I also gave Sernyl with a friend to a few rats. To our amusement, the animals started to walk backward!

WB: Did you publish your findings?

WB: We had two papers on Sernyl: one, in 1961, in the *Canadian Psychiatric Association Journal*, and another, few years later, in the proceedings of the fourth CINP Congress. My first paper on Sernyl, and my first paper based on my conditioning research appeared almost simultaneously. They were really my first “scientific” publications. WB: How did you get involved in conditioning?

TB: At the time I started my residency at McGill, we were still expected to prepare a thesis, based on some research, but mainly a literature review, to get our diploma in psychiatry. Since VPH had a conditioning laboratory, Dr. Lehmann, who was also my thesis supervisor, encouraged me to select a topic related to conditioning.

WB: When did you get your Diploma from McGill?

TB: In 1960, and I got it with distinction. Furthermore, on the recommendation of my examiners, my thesis was published with some modifications under the title, *Conditioning and Psychiatry*, by Aldine, in the United States, in 1964, and by Unwin, in the United Kingdom, in 1965. I had a Forward written by Horsley Gantt, the American disciple of Pavlov. Dr. Gantt apparently liked my thesis, and invited me to join his Society, the Pavlovian Society of North America. A few years later, in 1966, at the World Congress of Psychiatry in Madrid, I also became one of the founders of the Collegium Internationale Activitatis Nervosae Superioris (CIANS), an international society of people involved in conditioning research.

WB: Does that College still exist?

TB: Yes, but after Dr Gantt died, it was no longer the same College.

WB: When did he die?

TB: In 1980. He got seriously ill just a few weeks before a CIANS Congress in Milan and passed away soon after.

WB: Would you like to say something about your research in conditioning?

TB: From reviewing the literature, I got the idea that behavioral conditioned reflex (CR) variables might provide a bridge between psychopathology and neurophysiology. So, as soon as the thesis was completed, I developed a diagnostic test procedure based on the conditioning method using the eyelid closure technique. Then, in the 1960s, in collaboration with Drs. Lehmann and Bishan Saxena, a psychologist, we developed a conditioning test battery, the Verdun Conditioning Test Battery (VCTB), using several techniques to study psychopathological mechanisms and psychopharmacological effects. We also developed, in the 1960's, a psychometric test battery, the Verdun Psychometric Battery (VPTB) that included several perceptual, psychomotor, and other tests. Our interest was identifying predictors of treatment response to psychotropic drugs with the employment of these batteries. In the early 1970s, we published our findings in a monograph, *Experimental Approaches to Psychiatric Diagnosis*. Although I did not continue with research in conditioning after the mid-1970s, all through the years I have been thinking of resuming it. To acquire a CR is an innate property of the brain and our studies had indicated that CR variables, like acquisition, extinction, differentiation, reversal, etc., might provide a key to the understanding of the pathophysiology of abnormal mental functioning.

WB: What did you do after your residency?

TB: My residency was cut short because I was promoted from the first to fourth year, and in 1959, I became the junior member of Cameron's research team on "psychic driving." Ewen Cameron was chairman of psychiatry at McGill. He was one of the Nuremberg-psychiatrists and a past president of the American Psychiatric Association (APA).

WB: Would you like to say something about the research?

TB: The idea behind Cameron's research was that by wiping out all memories, one would also wipe out pathological patterns in the brain, and one might be able to rebuild the psyche anew. We also explored the possibility that it might be sufficient just to disorganize memories. For wiping out memories, we used regressive ECT, which Cameron referred to as "depatterning"; for disorganizing memories, we used psychomimetic drugs and sensory isolation, and for rebuilding, repetition of verbal signal therapy, which he referred to as "psychic driving." As the junior member of the team, I had to do whatever needed to be done, but my specific responsibility was the monitoring of changes in psychophysiological measures and CR variables. Today, what we did might sound rather unsophisticated, but it corresponded with the kind of research people did in those years. In our "sleep room," for example, where most of the research was done, in one bed a patient was treated by our team with regressive ECT, and in the next bed a patient was treated with "anaclitic therapy" by another research team, in which, grown-ups were mothered like babies. For me, still pretty much a foreigner in this new world, both treatments were rather strange, but the rationale for our experiment was at least as sound as the treatment used by the psychoanalytic group. In fact, we learned from our experiments that some patients with schizophrenia were not affected by sensory isolation, and also that wiped out obsessive-compulsive patterns re-emerge much sooner than memory returns. I left the team before it became public that the grant supporting our project came from the Society for Investigation of Human Ecology, a cover organization for the CIA. Cameron was vilified by the press, resigned, and died shortly thereafter, while mountain climbing. It was never completely clear whether he knew some of the money was from the CIA. I certainly did not. But even if he had known, I don't think he would have cared. Funds from the CIA were just as good as funds from anywhere else. He was interested in what he was doing and dedicated to help his patients.

WB: When did you get involved in drug studies?

TB: In the late 1950's. And, then, in the early 1960's, Jon Cole suggested to Dr. Lehmann to apply for a grant that would support an early clinical drug evaluation unit (ECDEU) at VPH, which, by that time was renamed, Douglas Hospital (DH). Lehmann was hesitant to pursue the matter, but when I expressed interest and willingness to direct the unit, we applied and our unit became one of the first in the program. So, during the 1960s and 1970s, we studied virtually all the psychotropic drugs that became available for clinical use in Canada and United States, and many others that never made it. I was told by Bill Guy, who was analyzing our data at the Biometric Laboratory of George Washington University, that we studied two or three times as many drugs as the other units in the program.

WB: Which were the drugs you studied?

TB: I think, cyclopentimine, a sympathomimetic alkylamine, and RP 8228, a phenylpiperidyl acetoxymethane, were the first drugs we published on.

WB: This was in the early 1960's?

TB: We studied these drugs in the late 1950's, before we set up our early clinical drug evaluation unit and published our findings in the early 1960's. When I first became involved with clinical investigations, it was a commonly held belief that inducing extrapyramidal signs (EPS) was a prerequisite for responding to neuroleptics. The newer neuroleptics induced more frequent and severe EPS, but contrary to the mainstream, in our hands, none of the newer drugs was any better than chlorpromazine. In fact, chlorpromazine appeared to be a more reliable treatment than any of its competitors. We conducted studies with "incisive neuroleptics," like prochlorperazine and thioproperazine, which were more potent on mg per kg basis in inducing both therapeutic effects and EPS, and also with "sedative neuroleptics," like methotrimeprazine, referred to as levomepromazine and chlorprothixene. Our findings with these drugs did not change our impression; "incisive neuroleptics" did not offer any real advantage over "sedative neuroleptics." There were differences in adverse effects, but not in therapeutic effects. In our conditioning studies, the effect of neuroleptics on the extinction of the orienting reflex seemed to be a more reliable predictor of whether a neuroleptic would work than the appearance of EPS.

WB: What about your findings with antidepressants?

TB: We were among the first to report on clinical findings with desipramine, the demethylated metabolite of imipramine, the first selective norepinephrine (NE) inhibitor. In our study,

desipramine did not seem to be a better antidepressant than imipramine or amitriptyline, the two antidepressants available at the time. So, we were somewhat puzzled when, a few years later, the catecholamine hypothesis of affective disorder was formulated. If the hypothesis was correct, desipramine should have been better than imipramine, the parent substance that had an effect on both 5HT and NE re-uptake. We were also involved, in the early 1960's, in studying trimipramine, a tricyclic compound which has no effect either on NE or 5-HT reuptake. It was just as good an antidepressant as any of the NE and/or 5-HT uptake inhibitors. Again, we were contrary to the mainstream. Those were exciting times, learning about these new drugs. We studied several tricyclic antidepressants; amitriptyline was more sedative than imipramine; desipramine had less anticholinergic side effects; trimipramine could safely be administered in combination with monoamine oxidase inhibitors; doxepin did not cause cardiac death in overdose, etc.

WB: You didn't have rating scales at the time?

TB: We used two scales from the very beginning, the Verdun Target Symptom Rating Scale and the Verdun Depression Scale, developed by Dr. Lehmann, in collaboration with Charlie Cahn and Roger deVerteuille for the first North American study of imipramine. We also used a comprehensive Psychopathological Symptom Check List (PSCL). But, for me, changes in the psychopathological symptom profile of individual patients were far more informative than changes in rating scale scores. In the early 1980's, to get more information than from conventional scales, like the Brief Psychiatric Rating Scale and Hamilton Depression Scale, we (in collaboration with Bill Guy) translated the AMDP and AGP Systems Manuals for the Assessment and Documentation of Psychopathology that were used in German speaking countries. At the same time, with a group of Italian psychiatrists in Pisa, we updated the ECDEU Assessment Manual, a collection of rating scales for use in clinical investigations, prepared by Guy and Bonato, in 1970.

WB: You were involved in the clinical development of how many psychotropic drugs? TB: Probably about 90. It would be difficult to recall by name all the drugs we studied. The list includes benzquinamide, butaclamol, butaperazine, clobazam, clomacran, clomipramine, clovoxamine, fluspirilene, flutroline, maprotiline, mesoridazine, mianserine, molindone, nomifensine, pimozone, propericiazine, viloxazine, and many others.

WB: Any observations or findings you would like to share?

TB: We noted carbamazepine's effect on mood in the mid 1960's, while studying it in epileptics; we had shown that nylidrine potentiates the effect of phenothiazines; we recognized the potential use of metronidazole in the treatment of alcoholism, of propranolol in organic agitation, and of naltrexone in controlling hallucinations in chronic schizophrenia; and we replicated Art Prange's findings with TRH in depression. In the late 1960's and early 1970's, we explored the possibility, with Dr. V.A. Kral, of using a pharmacological load test, such as 5% carbon dioxide inhalation, and intravenous injection of methamphetamine or sodium amobarbital in the prediction of therapeutic response in elderly patients to prototype psychotropic drugs, like methylphenidate, meprobamate, amitriptyline, thioridazine, nicotinic acid, and fluoxymeterone. We had numerous statistically significant findings, but none of them was of clinical significance.

WB: So, you had a special project in psychogeriatrics.

TB: We had a NIMH grant to study psychotropic drugs in the aged, while I was with McGill, and I continued with clinical investigations in the elderly during the Vanderbilt years. We were among the first, in the 1980's, to report favorable effects with nimodipine, a calcium channel blocker and choline alphospherate, a cholinomimetic substance in old age dementias. We had done several studies with Ateroid (glycosoaminoglycan polysulfate), a substance with heparinoid activity and I noted that it helped some patients with Alzheimer's and also some patients with vascular dementia.

WB: Did you publish all these findings?

TB: We presented and published most of our findings. In the early 1960's, together with a few colleagues interested in clinical investigations with psychotropic drugs in the Province of Quebec, we founded, the Quebec Psychopharmacological Research Association (QPRA), the predecessor of the Canadian College of Neuropsychopharmacology that provided a forum to discuss research findings. The proceedings of most of the QPRA symposia were published and made available. It was at a QPRA symposium, where we presented our findings in the first North American studies with haloperidol and triperidol. And it was also at a QPRA symposium, where we presented our findings in the first North American studies with chlorprothixene and clopenthixol. We were involved in the early years in side effect reporting to both the Canadian Health Protection Branch and the FDA. We thought that communicating some of the side effects we encountered was sufficiently important that we organized a QPRA symposium dedicated to skin pigmentation and ophthalmological changes seen in patients treated with high doses of chlorpromazine over a long

period of time. Another QPRA symposium dealt with thioridazine induced cardiac conductance changes. Our EKG studies with thioridazine were triggered by a report on two fatalities in the *Canadian Medical Association Journal* in 1963, and our findings reported, in 1964, in the same journal indicated that thioridazine produces a dose dependent prolongation of the QT interval that could lead to ventricular fibrillation. It might be relevant for the historical record that at the request of Sandoz, the Swiss drug company that manufactured thioridazine, we invited M.H Wendkos, a cardiologist at the Coatesville Veterans Administration Hospital in the United States, to our QPRA symposium, and he argued that the EKG changes with thioridazine were due to “benign repolarization disturbances.”

WB: You worked with Heinz Lehmann until when?

TB: From 1958 to 1976, while I was in Montreal but our collaboration continued after I went to Nashville. I started as his resident, then I became his Co-Principal Investigator, and when I was appointed Director of McGill’s Division of Psychopharmacology, he chaired our Board of Advisors. I think it was on his recommendation that I was asked to coordinate the Canadian Mental Health Association’s (CMHA) studies on *Nicotinic Acid in the Treatment of Schizophrenia*.

WB: Would you like to say something about those studies?

TB: It was a series of collaborative studies designed to replicate Abe Hoffer’s findings. But, as you probably know, we could not. Niacin was just not effective in the treatment of schizophrenia, regardless of whether it was given alone, or in combination with ascorbic acid or pyridoxine. There was no indication in our studies that niacin would augment the effect of neuroleptics either in acute or in chronic schizophrenic patients. We did not have a single patient who markedly benefited. To stop the nicotinic acid craze, which affected psychiatry in Canada more than any other country because Hoffer practiced in Saskatoon, our findings were widely publicized. They also found their place in the *American Psychiatric Association’s Task Force Report on Megavitamin Treatment in Psychiatry*. I was a member of that Task Force; Morrie Lipton, a distinguished past president of ACNP, was chairman.

WB: You mentioned McGill’s Division of Psychopharmacology. When was that established?

TB: In 1971. It was the first Division of Psychopharmacology in a University Department of Psychiatry. It started as a network of clinical investigators in seven McGill affiliated hospitals.

WB: So, we are now in the 1970s?

TB: Yes. Just about the time that the Division was established, I became Head of the Canadian Reference Center of the International Reference Center Network on Psychotropic Drugs. The Network was a joint effort between the Division of Mental Health of W.H.O. and NIMH, and it was coordinated by Alice Leeds from Washington. It was also the time, or might be a little bit later, that we started W.H.O.'s first training program for teachers of psychopharmacology. It was initiated by Gaston Castellanos, an officer in W.H.O.'s Division of Mental Health. We had several Fellows in that program annually from the early 1970's to the late 1980's. The first group of four Fellows was from Latin America: Ronaldo Ucha Udabe from Argentina, Luis Vergara from Panama, Carlos Zoch from Costa Rica, and Luis Galvan from Mexico. They were followed by Torres-Ruiz from Mexico and Imaz from Argentina. I had Júri Saarma, one of Kraepelin's successors as Chair of the Department of Psychiatry at the University of Tartu in Estonia, working with me for about a year with the Fellows. Soon after I moved to Nashville, the program moved with me and we had three Fellows, one after the other, from Czechoslovakia. Two of them, Jan Liebiger, and Eva Ceskova were to become professors of psychiatry, heads of university departments, after returning home, and one, Vaclav Filip, was to set up the first Clinical Research Organization (CRO) in that region. Then, we had Asano and Higano from Japan, Rudra Prakash from India, and Aitor Castillo from Peru. Among the last Fellows I had were Marek Jarema and François Ferrero. Marek was to become head and professor of one of the three psychiatric university clinics in Warsaw, and François was to become head and professor of the Department of Psychiatry at the University of Geneva.

WB: Could you say something about your W.H.O. program? What did the Fellows do?

TB: They participated in our activities and got experience in designing and conducting clinical drug studies, processing and analyzing data, and preparing reports.

WB: Did you keep contact with your Fellows after they left?

TB: I did, and developed research collaboration with most of them. In the late 1990's, we registered a research-company for the clinical profiling of psychotropic drugs.

WB: When did you move to Vanderbilt?

TB: In 1976.

WB: What was your position at Vanderbilt?

TB: I went there as director of the clinical research division of the Tennessee Neuropsychiatric Institute, a research facility on the premises of an old state hospital. Then, when the Institute was declared a fire hazard and closed, I continued at Vanderbilt as a tenured professor in the Department of Psychiatry, until becoming emeritus in the mid-1990s. From the Vanderbilt period, I spent two years, from 1981 to 1983, on an extended sabbatical in Geneva.

WB: What did you do in Geneva?

TB: I was consultant in psychopharmacology to the Division of Mental Health of W.H.O. During my first year, we carried out a “consensus study” among opinion leaders to find out their agreement how to use psychotropic drugs. So, we asked 28 opinion leaders with representation from five continents whether they agreed or disagreed with 32 treatment-related statements. We got a 100 percent consensus in response to four statements only. All OLs agreed that neuroleptics are indicated in the manic phase of manic-depressive psychosis; that long acting, depot neuroleptics should be used in the maintenance therapy of chronic schizophrenic patients who are unreliable about taking their medication; that amitriptyline has sedative effects, and that intravenous benzodiazepines are the treatment of choice for controlling status epilepticus. After returning to Nashville, I remained involved in consensus research with Mitch Balter and Uhli Uhlenhuth, until Mitch’s untimely death. Another project I initiated at W.H.O. was the development of an international network of clinical investigators, or more correctly a network of clinical research units, for the study of psychotropic drugs. My idea was to create a self supportive network from contracts with the drug industry for efficacy studies on new drugs, which would develop and implement a methodology for the clinical profiling of psychotropic drugs. Norman Sartorius seemed pleased with the idea of setting up the network, and Sandoz, was ready to sign our first contract. Bissy Odejide, one of my former W.H.O. fellows, at the time a professor of psychiatry at the University of Ibadan, Nigeria, agreed to direct the new program with me as consultant, and in a whirlwind trip, I traveled around the world from Cairo to Tokyo and Buenos Aires to identify prospective lead investigators in the network. By the time I returned to Geneva, the project was dropped; I never learned who blocked the project. It would have provided for worldwide clinical development of psychotropic drugs, a database that could have prevented confounding marketing with education about psychotropic drugs, and it might have generated feedback for pre-clinical research on developing rational treatments.

WB: Was there a central theme throughout your lifetime of research?

TB: The central theme of my research shifted during the years, from trying to find a common language for the pharmacodynamic action of psychotropic drugs and mental pathology, to trying to identify pharmacologically homogeneous populations within psychiatric diagnoses. The turning point was the publication of my text, *Psychopharmacology*.

WB: When was it published?

TB: It was published, in 1969, by Williams and Wilkins. I think it was the first book, in which psychopharmacology was presented as a discipline and not just therapy with psychotropic drugs. It was probably also the first book in which the development of psychotropic drugs is systematically reviewed from structure- activity relationships to clinical applications. The first part, General Psychopharmacology, is based on the material discussed at an ACNP Workshop, “What Preclinical Information Does the Clinician Expect to Be Given Prior to Conducting a Clinical Trial,” for which I tabulated all the information, i.e. brochures we received from the pharmaceutical company before starting a study with their drugs; the second part, “Systematic Psychopharmacology,” is based on a series of papers, published in *Applied Therapeutics*, in which all the information I was able to access about different groups of drugs, e.g., phenothiazines, benzodiazepines, in clinical use are reviewed; and the third, “Applied Psychopharmacology,” on the notes I used in teaching pharmacotherapy to psychiatric residents at McGill. It was in the “Closing Remarks” of *Psychopharmacology* that I first recognized the need to resolve the pharmacological heterogeneity within the diagnostic groups for neuropsychopharmacology to progress.

WB: How did you go about it?

TB: First, I thought that one might replace old diagnostic presuppositions by new diagnostic concepts, built from new building blocks, based exclusively on biologic criteria. But, by the mid-1980's, I recognized that biological measures have not shown to be anything more than epiphenomena of mental illness, and pharmacokinetic differences contributed little to the differential effect of psychotropic drugs. So, in a paper published, in 1987, I postulated that there is a clinical prerequisite for neuropsychopharmacological research; that the meaningfulness of biological, including psychopharmacological findings, depends upon whether they can be linked to a prior, valid diagnostic category based on psychopathology and psychiatric nosology.

WB: How did you get to this?

TB: I came across a paper by Frank Fish, a British professor of psychiatry, published in 1964, in *Encephale*, a French medical journal, in which, by re-classifying patients with schizophrenia using the method of Karl Leonhard, a German professor of psychiatry, he found a moderate to marked response to neuroleptics in more than 4 in 5 patients diagnosed as “affect-laden paraphrenia,” - a sub-population of “unsystematic schizophrenia,” characterized by delusions with intense emotional participation – and in less than 1 in 4 patients diagnosed as “systematic hebephrenia,” a subpopulation of “systematic schizophrenia.” Stimulated by Fish’s findings, we developed several instruments for identifying treatment responsive sub-populations that might be covered up by consensus-based diagnoses. These instruments include, *A Guide to Leonhard’s Classification of Chronic Schizophrenias (GUIDE)*, the *DCR (Diagnostic Criteria for Research) Budapest-Nashville for the Diagnosis and Classification of Functional Psychoses*, an instrument created in collaboration with Bertalan Pethö’s Hungarian team; *CODE-DD Composite Diagnostic Evaluation of Depressive Disorders*; and *CODE-HD Composite Diagnostic Evaluation of Hyperthymic Disorders*, developed in collaboration with Peter Gaszner, a Hungarian professor of psychiatry, while he was working with me in Nashville. *CODE-DD*, the prototype of the CODE System, was adopted and translated from English into Estonian, French, Hungarian, Italian, Polish, Portuguese, and Spanish.

WB: Would you like to say something about your findings?

TB: Our findings with the *GUIDE* and the *DCR* showed that the significantly different therapeutic response to neuroleptics in the two classes of schizophrenia reported by Fish, and also by Christian Astrup, is not restricted to therapeutic effects but applies also to adverse reactions. In an analysis of our international survey of about 800 chronic hospitalized schizophrenic patients, we found that tardive dyskinesia (TD) occurred more than three times as frequently in patients diagnosed, “systematic schizophrenia,” than in patients diagnosed “unsystematic schizophrenia.” Since, in Fish’s study, moderate to marked response to neuroleptics is more than three times as frequent in “unsystematic schizophrenias” than in “systematic schizophrenias,” the inverse relationship between therapeutic effects and TD indicates that the two classes of schizophrenia are pharmacologically distinct. Findings with *CODE-DD* indicate that DSM-III-R’s diagnostic concept of “major depression” is so broad that, using more stringent criteria, a large proportion of

patients would not qualify for a depressive illness. In one study, from over 300 patients only about one-third fulfilled CODE-DD's criteria of "melancholia," characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes. In another study of over 200 patients, less than one-fifth fulfilled Kurt Schneider's criteria of "vital depression," characterized by corporization, disturbance of vital balance, and feeling of loss of vitality. The discovery of the antidepressant effect of imipramine, as you know, was based on Roland Kuhn's findings in "vital depression." Our CODE-DD findings imply that those high prevalence rates of depression in epidemiological studies are irrelevant to neuropsychopharmacology. I had many discussions about our findings with Heinz Lehmann, before he passed away.

WB: He was a giant in the field. How old was he when he died?

TB: He was eighty eight.

WB: He was your mentor?

TB: I had two mentors. My first was Dr. Sandor, who introduced me into psychiatry, and my second mentor was Dr. Lehmann, who introduced me into psychopharmacology. As years passed, our working relationship evolved into a very close friendship.

WB: Before we run out of time, let me ask you a few specific questions. Where did the financial support for your research come from?

TB: NIMH, MRC (Medical Research Council) of Canada, the State of Tennessee, and from the drug industry. The development of CODE-DD was linked to the early clinical development of reboxetine and sponsored by Farmitalia supporting clinical investigations we conducted mainly with my former Fellows. By the 1990's, our research support from industry markedly decreased because I had no interest in participating in multi-center clinical investigations organized by CROs.

WB: Could you list what you think are your major findings?

TB: Well, I discovered that trazodone and reboxetine have antidepressant properties; that Ateroid might have therapeutic effects in old age dementias, but I don't consider those as major discoveries. My Psychopharmacology in the late 1960s, in which I systematically presented the action of psychotropic drugs at different levels, from molecular through neurophysiological and behavioral to translate pharmacological properties into clinical effects, I think was a major contribution that had an impact on the development of the field, even if that book is outdated by now and by and large forgotten. I consider my most important contribution the recognition of the

pharmacological heterogeneity within psychiatric diagnoses and developing methodologies for identifying more homogeneous populations in terms of psychopathology and psychiatric nosology. I also consider our conditioning test battery for the study of psychopathology and psychotropic drug effects, a contribution.

WB: So, all your work has been clinical, not basic?

TB: The answer is yes, even if during the 1960's, I was involved in some preclinical research with Drs. Kato and Gozsy, in exploring the effects of psychotropic drugs on dextran-induced capillary permeability. I found it interesting that one could predict whether a substance is an antipsychotic or an antidepressant from its effect on dextran-induced capillary permeability. Of course if anyone would have suggested testing a hypothesis that capillary permeability changes are the cause of depression or antidepressant effects, I would have been the first to object.

WB: Do you still see patients?

TB: I was seeing patients for well over forty years and used to pride myself that I had seen several times more patients than many practicing psychiatrists together, but my current activities don't leave me time to have even a part time practice.

WB: Tell me about the teaching experiences you've had.

TB: I was involved in teaching medical students, psychiatric residents, and fellows all through the years, supervising undergraduate and postgraduate students, and mentoring some of those interested in pursuing a career in our field. It was rewarding to see that *Psychopharmacology for Everyday Practice*, a book I published with Marc Hollender, was translated into Dutch and Japanese, and was used in teaching in those countries. And it has been most rewarding to see some of the Fellows trained in our W.H.O. program, becoming professors and heads of departments in their home countries.

WB: Your teaching had an international impact. Did you have administrative responsibilities?

TB: My first major administrative responsibility was directing McGill's Division of Psychopharmacology. The Division disintegrated shortly after I moved to Vanderbilt. And in the 1990's, I became President and Chairman of the Board of Directors of a company with my former associates that for all practical purposes died before it was born. It was probably unrealistic to form a company that was dependent on industrial support, which was trying to narrow the indications of drugs. So, I would say, I failed as an administrator.

WB: You always had an open mind, contrary to some people. You published extensively throughout the years. How many papers did you publish?

TB: Over seven hundred papers, including journal articles and book chapters.

WB: What was your last publication?

TB: “The Role of Serendipity in Drug Discovery.” It reviews the serendipitous discovery of many of the drugs used in psychiatry.

WB: Where was it published?

TB: In *Dialogue*, a journal published by Servier, a French drug company. I was very pleased to learn from Don Kline that he found it useful in preparing for his Oakley Ray history lecture this year.

WB: Were you involved in editing journals?

TB: I was co-editor with Fritz Freyhan and Pierre Pichot of the *International Journal of Pharmacopsychiatry*, and also of the series, *Modern Problems of Pharmacopsychiatry*.

WB: How many books have you written?

TB: Twenty three and edited twenty seven.

WB: So fifty altogether?

TB: Many of my edited books are collections of our studies with the same drug, e.g. trimipramine, trazodone, or drugs from the same family, e.g., butyrophenones, thioxanthenes. I used drug studies to generate information for a continuous re-evaluation of psychiatric concepts and many of my monographs are based on this continuous re-evaluation. *Schizophrenia, A Psychopharmacological Approach*, was followed by *Recent Advances in the Biology of Schizophrenia*, *Depression and the Tricyclic Antidepressants* was followed by the *Psychopharmacology of Depression*, and *Psychopharmacology in the Aged* was followed by *Cognitive Decline in the Aged*. My last monograph, *Classification of Psychoses*, was co-authored by Ronaldo Ucha Udabe, who was, as I said before, one of my former W.H.O. Fellows. He also co-edited with me, *The Neurotransmitter Era in Neuropsychopharmacology*, published in 2006.

WB: That’s very impressive. Can you say something about your family?

TB: I got married the day President Kennedy was assassinated. My wife is many generations Canadian. She is a graduate of the University of Western Ontario. She was a housewife until our son left for college, but after we moved to Toronto, she became an actress. Our son majored in

history and political science, then, after he got his Masters in European Community Law, he became a documentary filmmaker. He lives nearby in Toronto. We are a close knit family.

WB: What are your current activities?

TB: I am editing ACNP's ten volume oral history series on the first fifty years in the development of neuropsychopharmacology, which, in itself, is a full time job. It will complement CINP's four volume history series, I co-edited with David Healy and Edward Shorter, in which the same period was reviewed in autobiographical accounts. These two series should provide authentic, first-hand information on the birth and early development of neuropsychopharmacology. I am also serving on an independent commission of inquiry, set up by the Canadian University Teachers Association to find out what led to the seizure of the research files of a group of distinguished researchers by their Institute's ethics committee. We hope that by getting to the roots of the problem we would be able to make recommendations that could help prevent such a drastic measure being taken again. Finally, I have started to develop a new methodology I refer to as "nosologic homotyping" for identifying empirically derived pharmacologically homogeneous psychiatric populations. Nosologic homotypes are identical in psychopathologic symptoms, not in the content of symptoms of course, and are assigned the same position in the "nosologic matrix," based on three nosologic organizing principles, which are totality, temporality, and polarity. They are more homogenous in mental pathology and provide more suitable end-points for biological research than DSM-IV or ICD-10 diagnoses.

WB: I want to ask you one more question and that is about the future. What do you think is going to happen, both, in terms of your contributions or in terms of the field in the future?

TB: I believe we will identify pharmacologically more homogeneous populations in the next decades that will break the impasse of developing clinically more selective drugs, which in turn would open the path for molecular genetic research in psychiatry. I also believe that the identification of these populations will be based on research in psychopathology and psychiatric nosology and not in research on biochemistry, neurophysiology, endocrinology, or molecular genetics.

WB: Is there anything else you would like to add?

TB: I would like to add that while clinical research in conditioning has been dormant, basic research in conditioning continued and by the dawn of the 21st century, the structural and functional foundation of classical and operant conditioning have been discovered in the brain. So,

if it would be verified that the abnormal connections between and across mental structures, the structural basis of psychopathology, are CR connections, as some structural psychopathologists suggest, I could imagine, by letting my fantasy fly, that CR variables would provide a "code," something like the genetic code, that would define psychiatric disorders. The idea of course is not new. Its roots are in the research of Griesinger and Pavlov.

WB: Did I miss anything?

TB: I think we covered everything important and even some of my fantasies.

WB: I see you as being there from the very beginning, continuously active in research, writing a huge number of papers and books, and communicating across the different areas of our field. We talked about Heinz Lehmann, one of your mentors, being a giant. I think you also are a giant in this field. I really enjoyed talking with you and having a candid interview.

TB: Thank you. I enjoyed talking with you too.

APPENDIX 1: Curriculum Vitae of THOMAS A. BAN

Born: Budapest, Hungary, November 16, 1929
 Citizenship: Canadian (March 1, 1962)
 Family Status: Married (Joan Evelyn Valley)
 Son (Christopher)

EDUCATION:

Medical Student Budapesti Orvostudományi Egyetem (now Semmelweis University, Budapest, Hungary. 1948-1954
 Resident Psychiatrist Országos Ideg és Elmegyógyászati Intézet (National Institute of Nervous and Mental Disorders) Budapest, Hungary 1954-1956
 Clinical Fellow Montreal Neurological Institute, Montreal, Canada, (January-June) 1957
 Rotating Intern Victoria General Hospital, Halifax, Canada, 1957-1958
 Resident Psychiatrist Verdun Protestant Hospital (Douglas Hospital), Verdun, Canada, 1958-1959
 Allan Memorial Institute, Montreal, Canada, 1959-1960

CERTIFICATIONS, DIPLOMAS, LICENCES:

MD Budapesti Orvostudományi Egyetem (Semmelweis University), Budapest, Hungary, 1954
 LMCC Licensed Member of the Canadian Medical Council, 1959
 DP Diploma in Psychiatry with Distinction, McGill University, Montreal, Canada, 1960
 CPRC(C) Certification in Psychiatry, Royal College Physicians and Surgeons of Canada, November 12, 1962
 CPRC(QU) Certification in Psychiatry, College of Physicians and Surgeons, Province of Quebec, December 17, 1962
 FRCP(C) Fellow, Royal College of Physicians and Surgeons of Canada, October 12, 1972
 LMCP (QU) Licensed Member of the Corporation Professionnelle des Médecins du Québec, Montreal, 1962
 LMSTLB (USA) Licensed Member of the State of Tennessee Licensing Board for the Healing Arts, Nashville, 1976
 LMCP SO (ON) Licensed Member of the College of Physicians and Surgeons of Ontario, 1993

PROFESSIONAL EXPERIENCE:

A. Academic

Demonstrator	McGill University, Department of Psychiatry, Montreal, Canada 1960-1963
Lecturer	McGill University, Department of Psychiatry, Montreal, Canada 1963-1965
Assistant Professor	McGill University, Department of Psychiatry, Montreal, Canada 1965-1970
Associate Professor	McGill University, Department of Psychiatry, Montreal, Canada 1970-1976
Professor	Vanderbilt University, Nashville, Tennessee, USA 1976-1995
Emeritus Professor	Vanderbilt University, Nashville, Tennessee, USA 1995-

B. Administrative

Senior Psychiatrist Chief	Verdun Protestant Hospital, Verdun, Quebec, Canada 1960-1961 Clinical Research Service, Douglas Hospital, Verdun, Quebec, Canada 1961-1971
Director	Division of Psychopharmacology, McGill University, Montreal, Canada 1971-1976
Head	National Reference Center, World Health Organization Collaborating Reference Center Network for the Study of Psychotropic Drugs (Canada), Montreal, Canada 1972-1976
Director	WHO Training Program in Biological Psychiatry (WHO Collaborating Reference Center Network), Montreal, Canada 1972-1976
Director	Clinical Research Service, Tennessee Neuropsychiatric Institute, Nashville, USA 1976-1983
Director	Division of Psychopharmacology, Department of Psychiatry, Vanderbilt University, Nashville, USA 1983-1995
Chairman	FMCP, Toronto, Canada 1995-2004

C. Other Appointments

Consultant Psychiatrist, Lakeshore General Hospital, Pointe-Claire, Canada 1971-1986
Consultant, Division of Mental Health, World Health Organization, Geneva, Switzerland 1981-1983
Consultant Psychiatrist, Vanderbilt University Medical Center, Nashville, USA 1984-1995
Consultant Psychiatrist, VA Medical Center, Nashville, USA 1984-1995
Consultant Psychiatrist, Middle Tennessee Mental Health Institute, Nashville, USA 1984-1995
Consultant Psychiatrist, Vanderbilt Child and Adolescent Psychiatric Hospital, Nashville, USA 1989-1995

SCIENTIFIC SOCIETIES:

American College of Neuropsychopharmacology, Emeritus Fellow
American Medical Association, Member
American Psychiatric Association, Distinguished Life Fellow
Canadian Medical Association, Member

Canadian Psychiatric Association, Life Fellow
 Collegium Internationale Neuropsychopharmacologicum, Honorary Fellow (2002)
 Hungarian Psychiatric Association, Honorary Member
 Hungarian Association of Psychopharmacology, Honorary Member
 International Collegium of Composite Diagnostic Evaluation in Psychiatry, Honorary President
 International Wernicke-Kleist-Leonhard Society, Honorary Fellow
 The Argentine Association of Biological Psychiatry, Honorary Member
 The Societe Royale de Medecine Mentale de Belgique, Honorary Member

HONORS AND AWARDS

- Quebec Literary and Scientific Competition, 1965, Honorary Mention (Conditioning and Psychiatry, Aldine, Chicago)
- McNeil Award of the Canadian Psychiatric Association, 1969 (T.A. Ban, H.E. Lehmann and B.M. Saxena: A conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects Canadian Psychiatric Association Journal 1970; 15:301-308.)
- Clarke Institute of Psychiatry Annual Research Fund Award, 1970 (Psychopharmacology, Williams and Wilkins, Baltimore 1968)
- McNeil Award of the Canadian Psychiatric Association, 1970 (T.A. Ban and H.E. Lehmann: Nicotinic Acid in the Treatment of Schizophrenia. Progress Report I, Canadian Mental Health Association, Toronto 1970.)
- McNeil Award of the Canadian Psychiatric Association, 1973 (Nicotinic acid in the treatment of schizophrenia, Complementary Report A, Canadian Mental Health Association, Toronto 1973)
- Young Scientist Award of the Semmelweis Scientific Society 1975
- John F. Kennedy Medal of John F. Kennedy University of Argentina 1991
- Heinz E. Lehmann Research Award of the New York State of Mental Health 1996
- Paul Hoch Distinguished Service Award of the American College of Neuropsychopharmacology 2003

SCIENTIFIC PUBLICATIONS

Books authored: 26

Books edited: 30

Articles & book chapters: 700+

BOOKS AUTHORED

1. Conditioning and Psychiatry, Aldine, Chicago 1964; Unwin, London 1966
2. Psychopharmacology, Williams and Wilkins, Baltimore 1969
3. Pharmacotherapy of Tension and Anxiety, (H.E. Lehmann and T.A. Ban), Charles C. Thomas, Springfield, 1970

4. Nicotinic Acid in the Treatment of Schizophrenias. Introduction, Canadian Mental Health Association, Toronto 1970
5. Nicotinic Acid in the Treatment of Schizophrenias. Progress Report No. I, (T.A. Ban and H.E. Lehmann), Canadian Mental Health Association, Toronto 1971
6. Nicotinic Acid in the Treatment of Schizophrenias. Complementary Report A, Canadian Mental Health Association, Toronto 1971
7. Experimental Approaches to Psychiatric Diagnoses, (T.A. Ban and H.E. Lehmann), Charles C. Thomas, Springfield 1971
8. Schizophrenia: A Psychopharmacological Approach, Charles C. Thomas, Springfield 1972 (In the English original and in Japanese translation)
9. Recent Advances in the Biology of Schizophrenia, Charles C. Thomas, Springfield 1973 (In the English original and in Japanese translation)
10. Megavitamins and Orthomolecular Therapy in Psychiatry. American Psychiatric Association Task Force Report No. 7 (M. Lipton, T. Ban, F.J. Kane, J. Levine and R. Wittenborn), American Psychiatric Association, Washington 1973
11. Depression and the Tricyclic Antidepressants, Ronalds Federated, Montreal 1974
12. Introduction to the Psychopharmacology of Doxepin, Pfizer, Montreal 1977
13. Psychopharmacology of Thiothixene, Raven Press, New York 1978
14. Psychopharmacology for the Aged. Karger, New York 1980 (In the English original and in Japanese translation)
15. Psychopharmacology of Depression, Karger, New York 1981 (In the English original and in Italian translation)
16. Psychopharmacology for Everyday Practice. (T.A. Ban and M.H. Hollender), Karger, Basel 1981 (In the English original and in Dutch and Japanese translations)
17. Prolegomenon to the Clinical Prerequisite. Psychopharmacology and the Classification of Mental Disorders, Pergamon Press, Oxford 1987 (Progress in Neuro-Psychopharmacology and Biological Psychiatry 11: 527-580, 1987)
18. DCR Budapest-Nashville in the Diagnosis and Classification of Functional Psychoses. (B. Pethö and T.A. Ban in collaboration with A. Kelemen, G. Ungvari, I. Karczag, I. Bitter, J. Tolna, M. Jarema, F. Ferrero, E. Aguglia, G.L. Zurria, O.K. Fjetland) Karger, Basel 1988 (Psychopathology 21: 153-239, 1988)
19. CODE-DD. Composite Diagnostic Evaluation of Depressive Disorders, JM Productions, Nashville 1989 (In the English original and in Estonian, French, Italian and Polish translations)
20. Declino Cognitivo Nell'Anziano Demenza e Sindromi Demenziali Epidemiologia, Diagnosi Terapia, UTET, Milan 1991
21. Sostituire il Neurolettico, Il Pensiero. Scientifico Editore, Rome 1992
22. Clasificacion de las Psicosis, (T.A. Ban and R. Ucha Udabe) Salerno, Buenos Aires 1995
23. CODE-HD. Composite Diagnostic Evaluation of Hyperthymic Disorders, (P. Gaszner and T.A. Ban), Animula, Budapest 1998
24. Conditioning Behavior and Psychiatry. Aldine, London & New York 2008
25. Neuropsychopharmacology and the Forgotten Language of Psychiatry. Risskov: INHN; 2013: (Educational E-Books – November 14, 2013) (see inhn.org)
26. From Melancholia to Depression. A History of Diagnosis and Treatment. Risskov: INHN; 2014. (Educational E-Books – March 6, 2014) (see inhn.org)

BOOKS EDITED/TRANSLATED

1. The Butyrophenones in Psychiatry (H.E. Lehmann and T.A. Ban)
Quebec Psychopharmacological Research Association, Montreal, 1964.
2. Trimipramine, a New Antidepressant (H.E. Lehmann, M. Berthume and T.A. Ban),
Quebec Psychopharmacological Research Association, Montreal 1965
3. Toxicity and Adverse Reaction Studies with Neuroleptics and Antidepressants (H.E.
Lehmann and T.A. Ban), Quebec Psychopharmacological Research Association,
Montreal 1968
4. The Thioxanthenes (H.E. Lehmann and T.A. Ban), Karger, Basel 1969
5. Psychopharmacology, Sexual Disorders and Drug Abuse (T.A. Ban, J.R. Boissier, G.J.
Gessa, H. Heimann, L. Hollister, H.E. Lehmann, I. Munkvad, H. Steinberg, F. Sulser, A.
Sundvall and O. Vinar), North Holland, Amsterdam 1973
6. Trazodone (T.A. Ban and B. Silvestrini) Karger, Basel 1974
7. Drug Treatment of Sexual Dysfunction (T.A. Ban and F. Freyhan) Karger, Basel 1980.
Prevention and Treatment of Depression (T.A. Ban, R. Gonzalez, A.S. Jablensky, N.
Sartorius and F. Vartanian), University Park Press, Baltimore 1981
9. The AMDP-System. Manual for the Assessment and Documentation of Psychopathology
(translated and edited by W. Guy, T. A. Ban) Springer, Berlin 1982
10. Depression and Somatic Illness Pharmalibri, Morristown 1984
11. Amoxapine and Psychotic Depression. The Journal of Clinical Psychiatry Monograph
Series, Memphis (Volume 3, Number 1) 1985
12. The AGP System. Manual for the Documentation of Psychopathology in
Gerontopsychiatry
(Translated and edited by W. Guy, T.A. Ban), Springer, Berlin 1985
13. Assessment of Depression (N. Sartorius, T. A. Ban) Springer, Heidelberg 1986
14. Critical Issues in Psychology, Psychiatry and Physiology. A Memorial to W. Horsley
Gantt (J. McGuigan, T.A. Ban) Gordon and Breach, New York 1987
15. Thirty Years CINP (T. A. Ban, H. Hippus), Springer, Berlin, 1988
16. Diagnosis and Treatment of Old Age Dementias (T. A. Ban, H.E. Lehmann), Karger, Basel
1989
17. Functional Psychoses Today. (E. Aguglia, T. A. Ban), John Libbey, Rome 1991
18. Psychopharmacology in Perspective. A Personal Account by the Founders of the
Collegium Internationale Neuro-Psychopharmacologicum (T.A. Ban and H. Hippus),
Springer, Berlin 1992
19. Towards CINP. From the Paris Colloquium to the Milan Symposium (T.A. Ban, H.
Hippus), J. M. Productions, Brentwood 1994
20. Composite Diagnostic Evaluation System in Psychiatry. (P. Gaszner, T.A. Ban) Animula,
Budapest 1995
21. A History of the CINP (T.A. Ban, O.S. Ray), J. M. Productions Brentwood 1996
22. The Rise of Psychopharmacology and The Story of CINP (T.A. Ban, D. Healy, and E.
Shorter), Animula, Budapest 1998

23. The Triumph of Psychopharmacology and The Story of CINP (T.A. Ban, D. Healy and E. Shorter), Animula, Budapest 2000
24. CINP International Photo Archives in Neuropsychopharmacology 2000 (T.A. Ban, H. Beckmann, O. Ray), Animula, Budapest 2000
25. Gaszner Peter Valogatott Tanulmányai (G. Faludi, T.A. Ban) Animula, Budapest 2001
26. 26. From Psychopharmacology to Neuropsychopharmacology and The Story of CINP (T.A. Ban, D. Healy and E. Shorter). Animula, Budapest 2002
27. Selected Writings of Joel Elkes, Animula, Budapest 2002
28. An Early Attempt to Foster Neuroscience Globalization: An Autobiography by Erminio Costa (O. Ray and T. Ban), The Good Life Press, Nashville 2003
29. Reflections on Twentieth-Century Psychopharmacology (T.A. Ban, D. Healy, E. Shorter), Animula, Budapest 2004
30. The Neurotransmitter Era in Neuropsychopharmacology (T.A. Ban, R. Ucha Udabe), Editorial Pólemos, Buenos Aires 2006
31. An Oral History of Neuropsychopharmacology. Vol 1-10. American College of Neuropsychopharmacology, Brentwood 2011.

APPENDIX 2: Scientific contributions of THOMAS A. BAN

1. Recognition in the late 1950s that phencyclidine (Sernyl) accentuates existing psychopathological features (in doses of about 0.06-0.07 mg/kg) in psychiatric patients, and demonstration that in normal subjects and across psychiatric diagnoses it induces in lower doses, sensory-perceptual changes, and indifference, in higher doses. Phencyclidine was found to be unsuitable for use in chemically induced abreaactions but qualified for a psychotomimetic different from LSD₂₅ or psilocybin.

In the early 1980s it was shown that arylcyclohexylamines, like phencyclidine, selectively reduce the excitation of mammalian neurons induced by aspartate-like amino acids and neuropharmacological research with phencyclidine began.

2. Development of a conditioning test procedure and a conditioning test battery in the 1960s for the study of psychopathological mechanisms and psychopharmacological effects. The procedure/battery was employed in the description of psychiatric populations in terms of CR parameters and in clinical studies of predicting therapeutic responsiveness to neuroleptics in schizophrenia and to antidepressants in depression.

Ban TA. Conditioning and Psychiatry. Chicago, Aldine, 1964; London, Unwin 1966

Ban TA. Conditioning Behaviour and Psychiatry. London/New York, Aldine, 2008.

3. Contributions to the clinical development of psychotropic drugs used in the treatment of schizophrenia, depression, anxiety disorders, old age dementias and alcoholism from the late 1950s to the early 1990s:

1. amitriptyline: ECG changes
2. amoxapine: in suspicious & delusional depression
3. amoxapine & ethanol: driving skills
4. ascorbic acid: blood levels in chronic psychotic patients
5. benzhexol hydrochloride: toxic psychosis
6. benzoctamine
7. benzquinamide
8. bromperidol
9. butaclamol
10. butaperazine
11. BW 234U: antipsychotic effect (without blocking dopamine receptors)
12. carbamazepine
13. chlordiazepoxide: in prevention and treatment of alcohol withdrawal
14. chlorpromazine: *discovery* that high dose prolonged administration may produce skin pigmentation and ocular changes
15. choline alfoscerate: in old age dementias and after acute cerebral accident
16. CI-601
17. CIBA 30,802 Ba

18. clobazam
19. clomacran
20. clomipramine: in depression & OCD
21. clopenthixol: first clinical trials in North America
22. clovoxamine: sleep
23. cyclopentimine
24. desipramine: one of the first clinical trials & plasma levels
25. dextroamphetamine & meperidine: in the treatment of depression
26. diazepam
27. doxepin: in anxiety and depressive disorders; no EKG changes; increase in conflict tolerance
28. etafenoxin
29. EX 11-582A
30. EXP 561
31. fluoxymesterone: in psychogeriatrics
32. fluphenazine enanthate
33. fluspirilene
34. glycosaminoglycan polysulfate: *discovery* of possible therapeutic effect in primary degenerative dementia and in multi-infarct dementia
35. flutroline: dose determination
36. fluvoxamine: autonomic effects
37. haloperidol: first clinical trials in North America
38. haloperidol & chlorpromazine
39. hydroxyzine
40. levomepromazine (methotrimeprazine): agranulocytosis
41. lithium carbonate: teratogenicity, neurotoxicity
42. lithium & indomethacin & ibuprofen: interaction
43. lorazepam
44. loxapine: in psychogeriatrics
45. maprotiline: reversed catecholamine hypothesis of depression
46. mesoridazine
47. methionine & nicotinic acid: transmethylation hypothesis of schizophrenia
48. methyl dopa
49. metronidazole: in alcoholism
50. mianserin: dose determination; psychophysiological measures
51. MO 1255
52. molindone
53. naltrexone: in chronic schizophrenia with hallucinations
54. nicotinic acid: CMHA Collaborative Studies; failure to replicate findings
55. nicotinic acid & pyridoxine: CMHA Collaborative Studies; failure to replicate findings
56. nimodipine: *discovery* of possible therapeutic effect in old age dementias
57. nomifensine
58. nylidrine: *discovery* of potentiation of therapeutic effect of phenothiazines

59. penfluridol
60. pentylenetetrazol: in psychogeriatrics
61. phenelzine: ejaculatio retardata
62. prazepam
63. propranolol: in organic agitation
64. pimozide
65. piperacetazine
66. pipothiazine palmitate
67. prochlorperazine
68. propericiazine
69. protriptyline
70. protriptyline& perphenazine
71. R-806-003-01: plasma levels & therapeutic response
72. reboxetine: *discovery* of antidepressant effect; from dose determination to demonstration of efficacy
73. reserpine (NeSerp)
74. RP 8228
75. Senilex: in psychogeriatrics
76. thiopropazate
77. thioproperazine: demonstration that discontinuous treatment producing extrapyramidal shock offers no advantage to regular treatment
78. thioridazine: discovery and demonstration of a dose dependent reversible prolongation of QT interval (ECG)that may lead to ventricular fibrillation
79. thioridazine & fluoxymestereone: in psychogeriatrics
80. thioridazine & nicotinic acid: in psychogeriatrics
81. thioridazine & nicotinic acid & fluoxymestrone: in psychogeriatrics
82. thiothixene: systematic studies with special attention to activation & rapid tranquilization
83. trazodone: *discovery* of antidepressant effect; pharmacokinetics; from dose determination to demonstration of therapeutic efficacy
84. TRH: replication studies
85. trimipramine: antidepressant effect without blocking reuptake of NE/5-HT
86. troxonium tosylate: in drug-induced extrapyramidal symptoms
87. viloxazine
88. viloxazine& alcohol: psychomotor performance; driving skills
89. WIN 27,142-2
90. WY 3263
91. xanthine niacinate: in psychogeriatrics

A. Presentation of findings in systematic studies with some of these drugs (and of structurally similar drugs) in:

Lehmann HE, Ban TA eds. The *Butyrophenones* in Psychiatry. Montreal, Quebec Psychopharmacological Association, 1964

Lehmann HE, Berthaume M, Ban TA eds. *Trimipramine*. Montreal, Quebec Psychopharmacological Association, 1965

Ban TA, Silvestrini B eds, *Trazodone*. Basel, Karger, 1969

Ban TA, *Nicotinic Acid* in the Treatment of Schizophrenias. Introduction .Toronto, Canadian Mental Health Association, 1970.

Ban TA, Lehmann HE. *Nicotinic Acid* in the Treatment of Schizophrenias: Progress Report. I. Toronto, Canadian Mental Health Association, 1971.

Ban TA, Lehmann HE. *Nicotinic Acid* in the Treatment of Schizophrenias: Complementary Report A. Toronto, Canadian Mental Health Association, 1971..

Ban TA. Introduction to the Psychopharmacology of *Doxepin*. Montreal, Pfizer, 1977

Ban TA. Psychopharmacology of *Thiothixene*. New York, Raven Press, 1978

Ban TA. editor. *Amoxapine* in Psychotic Depression. The Journal of Clinical Psychiatry Monograph Series, Volume 3, Number 1, 1985

B. Presentation of findings in systematic studies of side effects (cardiac-conductance changes: thioridazine; skin pigmentation: chlorpromazine) in:

Lehmann HA, Ban TA. editors. Toxicity and Adverse Reaction Studies with Neuroleptics and Antidepressants. Montreal, Quebec Psychopharm. Research Association, 1968

C. Integration of preclinical and clinical findings with all psychotropic drugs from structure-activity relationships to clinical applications in:

Ban TA. Psychopharmacology. Baltimore, Williams & Wilkins, 1969, p. 485

“Psychopharmacology” is the first textbook in the field in which neurochemical, neurophysiological, and behavioral effects of psychotropic drugs are comprehensively reviewed in animal, normal subjects and psychiatric patients. It is divided into three parts: general psychopharmacology (includes methodologies used and findings in animal pharmacology, human pharmacology, clinical pharmacology and clinical investigations,) systematic psychopharmacology (includes the “systematic” presentation of findings in general psychopharmacology with barbiturates, amphetamines, phenothiazines, Rauwolfias, butyrophenones, thioxanthenes, tricyclic antidepressants, monoamine oxidase inhibitors, propanediols and benzodiazepines,) and applied psychopharmacology (includes pharmacological treatment of psychiatric disorders.)

D. Integration of findings with drugs used in the treatment of schizophrenias, depressions, old age dementias and anxiety disorders with findings in the literature, and re-evaluation of diagnostic concepts:

Lehmann, HE, Ban TA. *Pharmacotherapy of Tension and Anxiety*. Springfield, Charles C. Thomas, 1970

Ban TA. *Psychopharmacology of Schizophrenia*. Springfield, Charles C. Thomas, 1972

Ban TA. *Recent Advances to the Biology of Schizophrenia*. Springfield, Charles C. Thomas, 1973.

Ban TA. *Depression and the Tricyclic Antidepressants*. Montreal, Ronalds Federated, 1974.

Ban TA. *Psychopharmacology for the Aged*. Basel, Karger, 1980.

Ban TA. *Psychopharmacology of Depression*. Basel, Karger, 1981.

Ban TA, Lehmann HE eds. *Diagnosis and Treatment of Old Age Dementias*. Basel, Karger, 1989.

Ban TA. *Declino Cognitivo Nell'Anziano Demenza e Sindromi Demenzial Epidemiologia, Diagnosi e Terapia*. Milan, UTET, 1991.

E. Translation of findings in psychopharmacological research for practicing physician is presented in:

Ban TA, Hollender MH. *Psychopharmacology for Everyday Practice*. Basel/New York, Karger, 1981.

4. Recognition that the pharmacological heterogeneity within psychiatric diagnoses precludes the interpretation of findings in biological research in psychiatry and the provision of the necessary feedback for progress in neuropsychopharmacological research and the development of clinically more selective drugs (Closing remarks, Ban, *Psychopharmacology*, 1969, p. 431.)

Introduction of experimental (psychometric performance, conditioning and pharmacological load tests) approaches to complement, or replace psychiatric diagnoses in the study of psychotropic drugs.

Ban TA, Lehmann HE. *Experimental Approaches to Psychiatric Diagnosis*. Springfield, Charles C. Thomas, 1971.

5. Recognition that to date there is no alternative methodology to psychiatric nosology for classifying psychopathology in a clinically relevant manner:

Ban TA. Prolegomenon to the clinical pre-requisite Psychopharmacology and the classification of mental disorders. *Progress in Neuro-Psychopharmacology* 11: 527-580, 1987

6. Recognition that the current methodology used in clinical investigations for establishing therapeutic efficacy is unsuitable for identifying treatment responsive subforms (subpopulations) of illness (patients) and precludes the possibility for identifying these subforms (populations) by meta-analyses:

Ban TA. Academic psychiatry and the pharmaceutical industry. *Progress in Neuropsychopharmacology & Biological Psychiatry* 30: 429- 441, 2006.

Ban TA. Towards a clinical methodology for neuropsychopharmacological research. *Neuropsychopharmacologia Hungarica* 9: 81-90, 2007

A. *Translation and adoption of alternative instruments in the assessment of change to those included in Guy and Bonato's ECDEU (Early Clinical Drug Evaluation Units) Assessment Battery (NIMH, DHEW, 1970)*

Guy W, Ban TA. (translated and edited.) *The AMDP System. Manual for the Documentation of Psychopathology*. Berlin, Springer, 1982

Guy W, Ban TA. Translated and edited. *The AGP System. Manual for the Documentation of Psychopathology in Gerontopsychiatry*. Berlin, Springer, 1985

Development of instruments designed for resolving the pharmacological heterogeneity within the diagnoses of consensus-based classifications and identification of treatment responsive forms of illness:

Ban TA. Chronic schizophrenias. A guide to Leonhard's classification. *Comprehensive Psychiatry* 23: 155 – 165, 1983

Pethö B, Ban TA. DCR Budapest-Nashville in the diagnosis and classification of functional psychoses. *Psychopathology* 21: 153 – 239, 1988

Ban TA. CODE-DD Composite Diagnostic Evaluation of Depressive Disorders. Nashville, JM Productions, 1989 (In English original and in Estonian, French, Italian, and Polish translations)

Gaszner P, Ban TA. Composite Diagnostic Evaluation of Hyperthymic Disorders. Budapest, Animula, 1998

Findings with these instruments indicate that the DSM-III-R (also DSM-IV) diagnostic concept of

“major depression” is so broad that using more stringent criteria about 63 % to 80% of the patients would not qualify for depressive illness; Kraepelin’s diagnostic concept of “depressive states” is distinct from Schneider’s diagnostic concept of “vital depression”; and the diagnostic concept of “vital depression” (the diagnosis on which Roland Kuhn’s discovery of imipramine’s antidepressant effect was based) is covered up in the DSM-III- R (also in DSM-IV.) Similarly Leonhard’s diagnostic concept of “affect-laden paraphrenia” in which Frank Fish, in 1964, found that more than 4 in 5 patients show a moderate to marked response to neuroleptics is covered up in the DSM-III-R (also in DSM-IV.) Furthermore it was also shown that tardive dyskinesia occurred more than three times more frequently in patients with systematic schizophrenia a population in which about 1 in 4 patients respond to neuroleptics than inpatients with unsystematic schizophrenia in which in some populations (affect-laden paraphrenia) about 4 in 5 patients respond to neuroleptics; and that in 9 of 10 patients with unsystematic schizophrenia the addition of lithium to neuroleptics produced favorable effects, whereas in 9 of 14 patients with systematic schizophrenia the addition of lithium to neuroleptics produced unfavorable effects with toxic psychosis in 5 patients

7.Contributions to the reconstruction of the first fifty years in the development of neuropsychopharmacology

Ban TA, Healy D, Shorter E, editors. The History of Psychopharmacology and the CINP. As told in Autobiography. (4 volumes). Budapest, Animula, 1998-2004.

Ban TA, editor: An Oral History of Neuropsychopharmacology. (10 volumes). Brentwood, American College of Neuropsychopharmacology, 2011.

Ban TA, Ucha RU, editors. The Neurotransmitter Era in Neuropsychopharmacology. Buenos Aires, Polemos, 2006.

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