The Ten Volume Series of

An Oral History of Neuopsychopharmacology

The First Fifty Years

Peer Interviews

Editor:.Thomas A. Ban

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AN OVERVIEW OF THE FIRST FIFTY YEARS

Edited by Martin M. Katz

International Network for the History of Neuropsychopharmacology

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AN OVERVIEW OF THE FIRST FIFTY YEARS:

THE ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

Synopses by the 10 Volume Editors with Concluding Remarks by the Series Editor

Edited by Martin M. Katz

TABLE OF CONTENTS

Chapters

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INTRODUCTION

Martin M. Katz

Following the publication of the landmark ten volume series on the Oral History of Neuropsychopharmacology, Sam Gershon and I proposed to introduce the series to the membership of the American College of Neuropsychopharmacology (ACNP) via a Panel at their 2011 annual meeting. The idea for the 50-year History, recorded on videotape by the founders of the ACNP and by 213 participating members, was first proposed by our esteemed late Executive Director, Oakley Ray. He then left to Tom Ban, the task, who by a Herculean effort brought it to fruition. Tom monitored the collections, selected the interviewers and recruited the interviewees who responded with lively, engaging tales reflecting the origins and highpoints of a fascinating history in the development of a new science. To consolidate the effort Tom Ban divided the History into sectors covering the various participating sciences and periods of time and then, invited representative figures from those eras to edit each of the volumes.

There is no way to briefly summarize the some 213 interviews but we thought it highly useful to call to the attention of our membership the availability of this remarkable tour through the History of an exciting field. The members have been part of a revolution in the treatment and reconceptualization of mental disorders and have helped to open new vistas in the brain sciences.

In introducing the volumes, we asked for the purposes of the 2011 Panel, six of the Editors or a Representative of that era, to describe briefly the contents of their volumes. Later, in preparing this overview we decided it more appropriate to include brief descriptions of all of the volumes, so that the reader can not only receive the full picture, but also have a ready reference source from which to locate each and every one of the 213 interviews. Following each volume description, the chapter, includes a Table of Contents for that volume, identifying each of the interviewees and the interviewers

As always with such overviews, we seek to make ACNP members aware of this unique, valuable source for future research in our field and trust that they will find great satisfaction in reviewing their own, and their esteemed colleagues views and visions; perhaps, to ponder on how fortunate they were to have participated in this great adventure in science.

Chapter 1

Volume 1

STARTING UP

Edward Shorter

The first generation of psychopharmacologists and neuroscientists in this volume will someday have the status now accorded to Kit Carson and Zebulon Pike: They will be seen as opening up the drug treatment of illnesses of the mind and brain in the same way that the early pioneers opened the frontier of the West. The stories are comparable in drama: Before the Second World War, little was understood of the relationship between disease of the mind and brain and its treatment with drugs. Psychoanalysis was in the saddle, and a vast frontier lay unexplored.

Today, it is clear that certain mental diseases respond to pharmaceuticals – a terra incognita before the War -- and the mechanisms of drug action have started to be adumbrated, in a very tentative and uncertain way to be sure. But today we exclaim about how little we know about what we as yet don't know, as opposed to how little we know. This is a measure of three-quarters of a century of progress.

Consider the situation that prevailed in 1950. Sedatives had been available for half a century with the launch of the barbiturates; mild depressions had become treatable in the mid-1930s with the advent of the amphetamines. Yet the "Big C" of psychiatry, as Eli Robins at Washington University in St Louis called it, "craziness," or psychotic illness, remained unreachable. The serious mood disorders were untreatable save through electroconvulsive therapy, which had been originated only in 1938. And psychiatry had little to offer those with severe, disabling anxiety.

Change came rapidly in those "golden years," never again to be repeated: lithium was proposed for mania in 1949, chlorpromazine – the first antipsychotic – was clinically tested in

1952; the tricyclic antidepressants -- imipramine -- were first marketed in Switzerland in 1957. And the benzodiazepines surfaced with Librium (chlordiazepoxide) in 1960. These agents had a revolutionary impact. The field spun away from psychoanalysis and sprinted towards pharmacotherapies that were truly effective. Those who executed this pivot constitute the dramatis personae of this volume.

Len Cook recalls the development of chlorpromazine (CPZ) at Smith Kline and French in the mid-1950s. Thomas Detre, later chair of psychiatry at the University of Pittsburgh, remembers of his years at Yale that he proposed treating an agitated young female patient with chlorpromazine instead of psychotherapy – and the shocked silence that followed this suggestion. William Turner, on staff at Central Islip State Hospital on Long Island, remembered a female patient arriving "in a terrible state, accompanied by a husband who was tormented and distraught," then seeing her discharged several weeks later, after treatment with chlorpromazine, "radiant and buoyant with life." "Thorazine (CPZ), in just a couple of weeks, transformed this woman from the drab terrified person to a happy mother."

It is important to avoid the narrow nationalism that has informed much of the previous writing of this history. Many important drugs were developed in the United States but discovered in Europe. The ACNP is primarily an American organization, yet it numbers among its members such figures as the Hungarian Stephen Szara and the German Hans Hippius. Heinz Lehmann, who conducted early CPZ trials, was born in Germany, and Joel Elkes first saw the world in what is now Lithuania.

The volume is divided among Trialists, such as Frank J Ayd Jr, Leo Hollister, and Samuel Gershon; pharmacologists, such as Louis Lasagna; psychologists such as Joseph Brady and clinical scientists, including Alfred Freedman, Louis Gottschalk, and Joseph Wortis. These are all storied names, and there is no doubt in my mind that among future historians each will find his biographer (there were, alas, few females, among this pioneer generation; yet many came later).

The background of the interviewees varies widely. Some came to pharmacology via the Early Clinical Drug Evaluation Units (ECDEU) of the Psychopharmacology Service Center of NIMH, led by Jonathon Cole. Albert Kurland and William Turner numbered among these early

investigators. Others played a role in creating a clinical methodology appropriate for verifying the safety and effectiveness of the new drugs. Here Louis Lasagna helped to introduce the placebo-controlled randomized clinical trial that became the gold standard of verification, and Charles Jelleff Carr led studies in regulatory toxicology. At least four interviewees (Brady, Cook, Peter Dews and Larry Stein) pioneered behavioral pharmacology in studying the new drugs.

Readers will themselves encounter many other pleasures and surprises that await. This little talk serves merely to send up a flare: We are present at the start of the pioneers' trek towards the new and distant horizon of discovery in neuropsychopharmacology.

VOLUME ONE: INTERVIEWEES AND INTERVIEWERS

Trialists

Frank J. Ayd, Jr. interviewed by Leo E. Hollister
Samuel Gershon interviewed by Thomas A. Ban

Hanns F. Hippius interviewed by Andrea Tone

Leo E. Hollister interviewed by Frank J. Ayd, Jr.

Albert A. Kurland interviewed by Leo E. Hollister

Heinz E. Lehmann interviewed by William E. Bunney, Jr.

William J. Turner interviewed by Jo Ann Engelhardt

Pharmacologists

Joseph V. Brady interviewed by Leo E. Hollister

Charles Jelleff Carr interviewed by Thomas A. Ban

Leonard Cook interviewed by Larry Stein

Peter B. Dews interviewed by John A. Harvey

Edward F. Domino interviewed by Christian J. Gillin

Louis C. Lasagna interviewed by Donald F. Klein

Larry Stein interviewed by Arvid Carlsson

Clinical Scientists

Robert A. Cohen interviewed by Thomas A. Ban

Thomas Detre interviewed by Benjamin S. Bunney

Joel Elkes interviewed by Fridolin Sulser

Alfred M. Freedman interviewed by Thomas A. Ban

Louis A. Gottschalk interviewed by William E. Bunney, Jr.

Gerald J. Sarwer-Foner interviewed by A. George Awad

Stephen Szára interviewed by Leo E. Hollister

Joseph Wortis interviewed by Leo E. Hollister

Chapter 2

Volume 2

NEUROPHYSIOLOGY

Max Fink

The discovery of electricity in the mid-18th century was an exciting novelty that quickly led to its trials in medicine. By 1804 Giovanni Aldini and Benjamin Franklin had safely applied electric currents in melancholic patients, with seeming success. The motor cortex was electrically stimulated and mapped by Edouard Hitzig and Gustav Theodor Fritsch in 1870. Electric currents were observed from the surgically exposed brain of dogs in 1874 by English scientist Richard Caton. A half century later, in 1929, the German psychiatrist Hans Berger reported electric rhythms from the intact head of humans.

That electric rhythms permeated the brain brought brain structure and function front and center in the study of psychiatric illness. Mental and physical paradigms evoked passionate (although less bloody) arguments, similar to those that embroiled the wars of Catholics and Protestants. The conflicts between the somatic therapists and the psychoanalysts were deflected by a sudden enthusiasm for pharmacology that quickly dominated psychiatric practice and research. This science nurtured another compelling conflict, between those who believed that any animal regardless of its position in Nature's developmental tree was an appropriate model for man, and those who saw human pharmacology as sui generis, unique for the species and worthy of a focus in the science of man.

Berger modified the electrocardiograph, the instrument that recorded electrical activity of the heart, to amplify and record brain signals. He renamed it the electroencephalograph, giving neuropsychiatrist-clinicians a reliable measure of brain electrical activity in the living human. Studies of brain waves replaced neuropathology of the cadaver, the major tool of neuroscience in the 19th century. The electroencephalogram (EEG) was first applied to seizure disorders and to the newly introduced treatments of electroshock, insulin coma, and leucotomy. When psychoactive agents arrived in the clinics, this proven science of EEG was immediately applied

to record the changes induced by the new drugs. The clinicians who developed this science took two tracks: those who studied intact humans using scalp electrodes and those who implanted electrodes in the brains of animals to record cellular electrical activity.

Early in his work Berger recorded oscillating currents from the scalp of patients, reporting changes with vigilance, drugs, seizures, sleep and age. His 1929 publication Über das Elektroenkephalogramm des Menschen was followed by 12 additional reports, the last in April 1938. Tragically, Nazi laws forced his discharge from his hospital position with the loss of his laboratory. His successful suicide followed soon thereafter, another loss to German Nazism and anti-Semitism.

The EEG is markedly altered during and after induced seizures (ECT) and insulin-induced comas (ICT). The changes are progressive and persist for weeks after the last treatment. Recordings are painless, can be repeated without risk, and are sensitive to moment-to-moment changes in brain physiology. In the 1950s, the EEG effects of ECT were reported by ACNP members Herman Denber, Joel Elkes, Max Fink, Sidney Merlis, and George Ulett, and it was relatively easy to apply the same instruments and methods to study the new psychoactive agents as they were introduced.

Presentations at international conferences in Paris in 1957 and the CINP meeting in Rome in 1958 introduced clinicians to the new science. In a memorable session in Rome, Turan Itil and Dieter Bente described their experience with chlorpromazine (CPZ) and imipramine (IMI) from their Erlangen laboratory. Each medication had distinguishable effects on EEG frequencies and amplitudes. CPZ elicited seizure activity, while IMI did not. After their presentation, Max Fink from New York City's Hillside Hospital described the same findings for the same medications. This immediate independent replication established a science of pharmaco-electroencephalography (pharmaco-EEG) that flourished for three decades.

Human pharmaco-EEG studies

EEG laboratories were widely established in the asylums in the 1940s. The effects of amobarbital and amphetamine, the seizures of ECT, and the comas of ICT were already well described when LSD, then chlorpromazine, meprobamate and imipramine startled the clinicians with their effects in the severely ill.

Psychoactive agents – substances that cross the brain's blood-brain barrier and alter the fluids bathing brain cells – influence the frequencies, amplitudes, and patterns of waveforms in the resting EEG of alert subjects. The effects of chronic treatment and acute intravenous administration were catalogued in patients, and then in normal adult volunteers. At first, these changes in electric patterns were considered specific for individual chemicals, but as more substances were studied, class-specific patterns emerged. The EEG effects of substances clinically identified as "antipsychotic" differed from those considered "antidepressant" or "psychostimulant." The EEG signatures of hallucinogens, deliriants, and anxiolytics added to the identifiable patterns. The chemicals that failed to influence brain electrical activity were found to be clinically inert, no more effective than placebos."[,,,]

The first studies scanned paper records by page turning, seeking identifiable patterns and estimating the changes in frequencies and amplitudes using clinical guidelines. To assure quantitative measurements, electronic analyzers and then digital computer analyzer systems were developed and applied. Max Fink and Turan Itil used successively improving digital computer analyzers to measure changes in frequency and electric power and to measure drug effects across the spectrum of psychoactive drugs. Amplitude analysis was applied by Arthur Sugerman working with David Engelhardt, Carl Pfeiffer and Leonide Goldstein. Sam Kaim examined the effects of addicting substances, the minor tranquillizers, alcohol, opioids, and opioid antagonists. Herman Denber, Sidney Merlis and Sidney Malitz characterized different compounds in their clinical studies of new drugs in asylum populations.

Itil's laboratories in St. Louis and New York became the principal training center for the pharmaco-EEG leaders, with Werner Herrmann in Berlin, Bernd Saletu in Vienna, Masami Saito in Japan, Sevket Akpinar in Turkey, and Jovan Simeon in Ottawa as graduates. Their assays defined many new active drugs developed in their countries' laboratories.

The sleep EEG was the focus of interest of Irwin Feinberg, Ernst Hartmann, Chris Gillin, Enoch Callaway and Turan Itil. As a science of evoked electrical potentials developed, Callaway and Itil described the effects of psychoactive drugs on this measure of brain electrical activity.

The Association-Dissociation controversy.

Did the EEG reflect differences in clinical changes with psychoactive drugs, or were the measured changes epiphenomena of limited clinical significance? Human studies reported

different EEG patterns for antidepressant, antipsychotic and anxiolytic drugs. These observations were formulated in a hypothesis of the association of EEG and behavior. Pharmacologists working with animals reported no such relationship and formulated a dictum of dissociation between the EEG and behavior. Since much of industry support for pharmacology was based on the assumption that the studies could predict human effects, the clinicians' challenge required a strong defense to justify the expensive experimentation and destruction of animals.

In the mid-1960s these different experiences were presented at meetings of the ACNP, CINP, SBP, and EEG Societies. The pharmacologists described anticholinergic drugs as eliciting "sleep EEG" records with high voltage burst activity in dogs, cats, rabbits and monkeys when the animals were restless with running motor movements. Examined closely, these animals were not "sleeping" but were delirious. They were neither able to carry out learned commands nor to make their usual responses to sensory cues. Their EEG showed a preponderance of fast frequencies and a lack of patterned sleep stages. The dissociation reported by pharmacologists resulted from their limited range of observations – limiting measures of behavior to motor functions only, and limiting the EEG to visual measures of the superficial similarity between the EEG of normal sleep to that occurring in delirium.

The assumption of a direct predictive relationship between findings in animals and humans ignores species differences in brain chemistry developed during evolution. The brain is well shielded from external injury by the skull and meninges, and internally by a physiologic blood-brain barrier that excludes foreign substances from impacting brain cells. Each animal species is unique in what it allows through these barriers, a resultant of the millennia of differences in feeding patterns and exposures to toxic agents. Evolution influences the responses and tolerance of species to potential chemical toxins. A well-known example of species specificity is the opioid induction of excitement in felines but sedation in bovines, primates, and man. The ability of animal breeders to develop genetic lines that are either seizure-prone or seizure-tolerant to noise and light is a classic example that is commonly used in selecting animals for study. I observed the differential tolerance of beagles and setters to anticholinergic deliriants. Species differences challenge the accepted pharmacology fallacy that animals are automatic surrogates for man. Species dissociations in psychopharmacology are a warning that predictions for humans from observations in animals are at the scientist's and society's hazard.

Laboratory neurophysiology.

By mid-century technological advances had made possible the recording of electrical oscillations from the brain surface, then clusters of cells, then from individual cells. Chemicals were first applied by massive dosing through oral and parenteral routes and then by localized administration to single or a few contiguous cells. After working with Joel Elkes at St. Elizabeth's Hospital, Floyd Bloom developed micro-iontophoresis techniques to study drug effects in cats and rabbits. The metabolism of the cyclic AMP and noradrenaline systems, and the effects of endorphins, opioid peptides, alcohol, and almost all psychoactive chemicals were catalogued. His neuropharmacology texts describing these technical achievements became standard college teaching vehicles.

Extensive single neuron cell recordings by George Aghajanian at Yale, Philip Bradley in the UK, Vincenzo Longo in Italy, and Eva and Keith Killam at various sites in California extended our knowledge of various substances on the electrical firing rates of neurons. The effects of marketed psychoactive drugs on the many neurotransmitters were elegantly detailed, offering a confusing catalog of drug effects. The transmitter hypothesis of CNS active drug effects is elaborate but so far has been poorly related to human behavior.

The contributions of Philip Bradley are illustrative. After studying the human EEG with Grey Walter at Burden Neurological Institute, and describing the effects of LSD in man, Bradley turned to single cell recordings in animals. His examination of atropine and physostigmine led him to support the dissociation hypothesis of Abraham Wikler that the behavioral consequences of these drugs were not related to their EEG effects. He was the principal protagonist in the controversy that is defined in the conference proceedings published in 1968 cited earlier.

In addition to depth recordings, the Killams developed a baboon model of epilepsy, following the work of Robert Naquet of Marseilles. Keith Killam was active in computer analysis early in the era, building a LINC computer. Later he developed telemetry systems to monitor free-ranging animals. Studying flicker-evoked seizures, the Killams studied the relative potencies of anticonvulsants.

Brain structure imaging.

Soon after the discovery of X-ray, recordings pictured the skull and its defects. With air injected into the spinal canal as a contrast substance, shadows of the ventricles were seen

(pneumo-encephalography). Carotid angiography, a technique developed by Egas Moniz and for which he received the Nobel Prize in Medicine in 1949, illustrated the brain's vascular circulation. Both techniques were painfully invasive and risky. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) offered less invasive images of brain activity. ACNP members Nancy Andreasen, José Delgado, Philip Holzman and Robert Kessler applied these imaging systems to studies of patients.

Nancy Andreasen examined the relationship between symptom patterns of schizophrenic patients – the positive and negative symptoms – and brain structure. Her studies defined loss of brain structure as a marker for chronic psychosis.

Abnormalities in eye movements are found in the severe mentally ill. Philip Holzman reported abnormalities in pursuit eye movements and diminished vestibular nystagmus as a marker in psychotic patients and in their first-degree relatives. José Delgado began with animal studies of lobotomy and implanted electrodes demonstrating that stimulation of specific brain loci has identifiable effects on the animal's movement and attack behavior. His dramatic demonstration of control of a charging bull in a bullfight arena startled the public.

Prologue or epilogue?

After more than eighty years of studies of the impact of chemical agents on the electrical rhythms in man what have we learned? The blood-brain barrier is selectively permeable to many chemical substances that alter the electrical and chemical activity of brain cells, thereby altering behaviors. These are the "psychoactive" substances. Chemicals that do not breach this barrier are inert in their influence on behavior.

Do the changes in electrical rhythms relate to the interpersonal behaviors that challenge clinicians? Apparently yes; some chemicals alter brain rhythms, motor behavior and vigilance in predictable fashions. In man, we associate the EEG changes with changes in mood, orientation, and thought, and we have achieved success in predicting clinical drug effects. Agents that affect the human brain are identified, and the variations in EEG rhythms are associated with specific behaviors. Agents that elicit hallucinations and delusions with clear orientation are distinguished from deliriants that affect thought as well as orientation, and from those that minimize or inhibit such thoughts. Some agents alter mood; some increase motor activity while others inhibit and sedate. For each behavior, the change in EEG pattern bears a predictive relationship.

Electrically-induced seizures produce slow frequencies and increase amplitudes of resting EEG rhythms. These changes are necessary accompaniments to assure behavioral change. Patients who do not show systematic EEG change do not change their behavior. Is the same true for antidepressant, anxiolytic or antipsychotic agents? We believe so, but we have lost both clinical and research interest to document this relationship.

Alas, the effects of drugs on brain rhythms are species sensitive. Explanations based on neurotransmitter measures, especially when these are recorded in animals, have not been helpful. Similarly, the connections between single cell recordings and human behavior have been elusive. The present brain imaging methods are too gross to define the subtle changes in behavior that interest psychiatrists and neurologists. Of these technologies – brain imaging, single cell recordings, EEG recordings in animals and in humans – we are left with the thought that the scalp recorded EEG in man is still the most promising instrument for understanding the effects of psychoactive drugs. Recordings using scalp electrodes are not invasive, are sensitive to moment-to-moment chemical and behavior changes, and may be repeated as often and for as long as the researcher wishes. The stories embedded in these interviews teach readers that more detailed studies are warranted. Sadly, the pharmaco-EEG methods of alert and sleeping patients that are exquisitely measurable by digital computer analytic methods are no longer active areas of inquiry.

VOLUME TWO: INTERVIEWEES AND INTERVIEWERS

PART ONE: *Electrophysiology and Neuropsychopharmacology*

Clinical Research

Enoch Callaway III interviewed by Thomas A. Ban

Turan M. Itil interviewed by Thomas A. Ban

Samuel C. Kaim interviewed by Leo E. Hollister

A. Arthur Sugerman interviewed by Thomas A. Ban

Irwin Feinberg interviewed by Leo E. Hollister

J. Christian Gillin interviewed by William E. Bunney, Jr

Ernest Hartmann interviewed by Thomas A. Ban

Chapter 3

Volume 3

NEUROPHARMACOLOGY

The Neurotransmitter Era

Fridolin Sulser

This volume contains autobiographical sketches and insight into contributions to neuropharmacology by some of the founders of our field as it developed from classical neuropharmacology to molecular neurobiology. To do justice, each one of the 33 interviews would require at least 10 min. for discussion of their scientific contributions to neuropharmacology. This would amount to approximately 5 1/2 hours. I have 10 minutes! However my introduction and dramatis personae section and Tom Ban's preface to volume 3 honors, in an abbreviated form, contributions of the 33 interviewees of this volume. This volume is dedicated to Bernard B. Brodie because, historically, the most pertinent catalysts of scientific progress in our field has been the "Brodie school" with its first and second-generation pupils (Julian Axelrod, etc.). Four contributors to this volume, 3 Brody pupils, Axelrod, Carlsson and Greengard, and Eric Kandel, received in 2000 the Nobel Prize for their pioneering research!

The current research in our field is firmly based on research contributions made by these 33 pioneers in neuropharmacology during the late 1950s, the 60s and 70s. The contributions to this volume are testimony to the importance of the role of new methodologies in advancing science. It is these new methodologies that have catalyzed the birth of the Neurotransmitter Era in neuropharmacology. Thus, the invention of spectrofluorometric methodology by Bowman and Udenfriend in Brodie's Laboratory of Chemical Pharmacology in the early 1950s made it possible to analyze quantitatively minute amounts of biogenic amines in brain. Using this new methodology, Pletscher, Shore and Brody demonstrated in 1956 that reserpines's tranquilizing action is associated with a dose-dependent depletion of brain serotonin. This was a historic finding as it catalyzed world-wide research on the neurobiology of monoamines, for example, dopamine (DA), norepinephrine (NE), serotonin (5-HT). Another powerful technique fluorescent

histochemistry, developed by Falck and Hillarp, made it possible for Kjelle Fuxel, Annika Dahlstrom and Arvid Carlsson to study putative neurotransmitters, DA, NE and serotonin and their regulation at the cellular level. The Swedish group represented in this volume discovered the nigro–striatal, the mesolimbic and the tubero-infundibular dopamine system. They mapped the major ascending and descending brainstem NE systems and the brainstem. serotonin systems. And Huda Akil with her husband Stan Watson employed in a series of elegant studies immunochemistry to map the anatomy of the endorphin system and of dynorphin in brain.

A 3rd revolutionary advance was the availability of radioactive isotopes. Using tritiated norepinephrine, Axelrod discusses in this volume the important discovery of the pre-synaptic reuptake of biogenic amines in peripheral and central monoaminergic neurons as a means to terminate the biological response of synaptic ally released norepinephrine, dopamine, and serotonin. This discovery was followed by the finding that tricyclic antidepressants enhance noradrenergic activity by blocking the neuronal reuptake of norepinephrine in peripheral and central nor-adrenergic neurons. Then, Carlsson demonstrated that tricyclc antidepressants also inhibited the reuptake of 5HT into central serotonergic neurons with tertiary amines oi tricyclics being more potent in blocking the reuptake of 5HT than the corresponding secondary amines and secondary amines being more potent in inhibiting the reuptake of NE. Besides providing simple screening techniques for the discovery of new antidepressants, these findings contributed further to the clinically relevant monoamine hypotheses of depression. The sophisticated use of radiolabeled agonists and antagonists and the rapid filtration technique of Cuatrecasas led to the discovery of the opiate receptor by Candice Pert and Sol Snyder, the discovery of subtypes of serotonin and dopamine receptors. Elaine Sanders-Bush was actually one of the 1st ones to suggest that multiple serotonin receptors exist. The amazing discovery by Sol Snyder of nitric oxide in brain changed all the rules about neurotransmission. One of the most exciting findings using a radioimmune assay is the discovery of endogenous morphine in brain by Sidney Spector. James V. Dingell's research demonstrates the power of solvent extraction procedures and quantitative fluorametric analysis of drugs and their metabolites in brain and other tissues. The studies by Irv Kopin contributed significantly to the understanding of catecholamine metabolism and the role of false transmitters. Wurtman and Axelrod elucidated the function of melatonin and diurnal rhythm of pineal gland function. Inspired by the studies carried out by Earl Sutherland on cyclic AMP, synaptic transmission was carried beyond the receptors to 2nd messenger mediated

cascades. Paul Greengard discusses eloquently in this volume the neurobiology of neurotransmitter mediated signaling and the importance of 2nd messenger mediated protein kinase activation. His studies on dopamine sensitive adenylate and the phosphorylation by cyclic AMP stimulated protein in kinase A of substrates such as DARP 32 as a bifunctional molecule, its function dependent on the site of phosphorylation of theonine–are classics in the molecular neurobiology of signal transduction. He establishes that protein phosphorylation is the major molecular event causing changes in signal transduction in brain. Beside the activation of the dopamine sensitive adenylate cyclase, mediated by the D1 subclass of DA receptors there are now known several neurotransmitters sensitive adenylate cyclase. The discovery of the coupling of various receptors via G-proteins to adenylate cyclase.or guanylate cyclase, forming the 2nd messengers cyclic AMP or GMP respectively, was a major advance in the elucidation of principles of slow synaptic transmission. It seems now very likely that all of the biogenic amines and all of the peptide neurotransmitters exert their effects on their target cells through slow synaptic transmission.

With regards to the action of psychotropic drugs on noradrenergic transduction, Alan Frazer, our present secretary of the ACNP and Jerzy Vetulanit in my laboratory, were the 1st investigators to use chronic treatment on a clinically relevant time basis. They discovered that chronic, but not acute treatment with tricyclic antidepressants down regulates the beta-adrenergic cyclic AMP system in brain. Our group at Vanderbilt then demonstrated that antidepressant treatment, including electroconvulsive treatment (ECT), if applied on a clinically relevant time basis, caused a net deamplification of the norepinephrine signal.

Conceptually the studies switched the emphasis in understanding the mode of action of antidepressants and the pathophysiology of affective disorders from acute presynaptic to delayed postsynaptic 2nd messenger mediated events. They opened the gateway for subsequent studies of events beyond the receptors including changes in programs of gene expression. Eric Kandel has beautifully analyzed the molecular biology of memory storage using his classical aplysia model. His studies provided the 1st molecular insight into the process of learning. The goal of Sam Barondes' research activities has been bringing molecular biology to psychiatry. He has discovered a number of lectins that play a role in cell interactions. Stephen Paul's recent research is focused on Alzheimer's disease exploring the role of genes that facilitate amyloid deposition in brain, for example apolipoprotein E. Merton Sandler and Moussa Youdin demonstrated multiple

forms of monamine oxidase (MAO).

The Neurotransmitter Era in neuropharmacology has also witnessed the arrival of new drugs, for example imipramine by Roland Kuhn, meprobamate by Frank Berger, iproniazid and synthetic benzoquinolizines by Alfred Pletscher, the MAO B inhibitor deprenyl by Joseph Knoll and aripiprazole, sumatripan and zolpidem by Salomon Langer.

In conclusion it is fair to say that collectively, the interviewees in this volume have been responsible for the epochal changes in neuropharmacology and neuroscience in general.

Besides the scientific contributions by the 33 interviewees, their autobiographic sketches contain many delightful personal stories. As the Editor of volume 3, I tremendously enjoyed reading the interviews and I'm sure you will likewise enjoy them!!

VOLUME THREE: INTERVIEWEES AND INTERVIEWERS

Bernard W. Agranoff, interviewed by Leonard Cook
Huda Akil, interviewed by James H. Meador-Woodruff
Julius Axelrod, interviewed by Leo E. Hollister
Jack D. Barchas, interviewed by Stanley J. Watson
Samuel H. Barondes, interviewed by Andrea Tone & Thomas A. Ban
Frank M. Berger, interviewed by Leo E. Hollister
Arvid Carlsson, interviewed by William E. Bunney, Jr.
Annica Dalhstrom, interviewed by Andrea Tone
James V. Dingell, interviewed by Leo E. Hollister
Salvatore Enna, interviewed by Elizabeth Bromley
Hans Christian Fibiger, interviewed by Thomas A. Ban
Alan Frazer, interviewed by Stephen H. Koslow
Kjell Fuxe, interviewed by Thomas A. Ban
Silvio Garattini, interviewed by Leo E. Hollister
Paul Greengard, interviewed by Eric J. Nestler
Leslie L. Iversen, interviewed by Thomas A. Ban
Murray E. Jarvik, interviewed by Thomas A. Ban
Eric R. Kandel, interviewed by Huda Akil
Alexander G. Karczmar, interviewed by Erminio Costa

Joseph Knoll, interviewed by Thomas A. Ban

Irwin J. Kopin, interviewed by Thomas A. Ban

Hrbans Lal, interviewed by Elizabeth Bromley

Salomon Z. Langer, interviewed by William E. Bunney, Jr.

Steven Marc Paul, interviewed by Thomas A. Ban

Candice B. Pert, interviewed by Leo E. Hollister

Alfred Pletscher, interviewed by Thomas A. Ban

Paul Ronald Sanberg, interviewed by Matthew J. Wayner

Elaine Sanders-Bush, interviewed by Joel Braslow

Merton Sandler, interviewed by David Healy

Solomon H. Snyder, interviewed by Floyd E. Bloom

Sydney Spector, interviewed by Fridolin Sulser

Fridolin Sulser, interviewed by Leo E. Hollister

Richard J. Wurtman, interviewed by Thomas A. Ban

Chapter 4

Volume 4

PSYCHOPHARMACOLOGY

(Editor: Jerome Levine)

Barry Blackwell

In the Preface to Volume 4, “Psychopharmacology” the series editor, Tom Ban, explains this is the final one of the first four volumes of the OHP series each of which deals with a different aspect of “psychopharmacology”; Behavioral pharmacology (Volume 1), Neurophysiology (Volume 2), Neuropharmacology (Volume 3) and now Clinical Psychopharmacology (Volume 4). The latter deals with changes in mental faculties and psychopathology brought about by drugs with emphasis on the measurement of outcomes (rating scales and assessment instruments) together with categorization of response entities (nosology).

In his preview of the field Ban identifies two seminal methods developed to accomplish these evaluative goals in the 1950’s and 1960’s; the AMP system originating in Germany and Switzerland and the BLIPS developed in the United states by the Psychopharmacology Service Center at the National Institute of Mental Health (NIMH) and utilized by the Early Clinical Drug Evaluation Units (ECDEU). The evolution and characteristics of these two systems are described including the standardization of rating scales and statistical analysis. This is followed by the ontology of the American Psychiatric Association’s DSM system of consensus based diagnostic classification, culminating in the multiaxial system of DSM III.

Volume 4 includes thirty interviews, twenty-three are M.D’s (22 psychiatrists and 1 general practitioner) and seven are Ph.D.’s (6 psychologists and 1 social worker).

The Volume is dedicated to Arnold J. Friedhoff, ACNP President in 1978, a neuropsychopharmacologist who did early work on the “pink spot” (DMPEA) in schizophrenia,

proposed the “dopamine hypothesis” and worked on the genetics of schizophrenia. His OHP interview by Steve Bunney is in Volume 5. Dr. Friedhoff died in 2001.

In a brief introduction the Volume Editor, “Jerry” Levine notes that the fifty year history of psychopharmacology began with serendipitous clinical observations of the way chemical compounds benefited mental illness which “drove the field to prove that the changes were real and to understand the mechanisms involved”. Jerry notes, “the nuanced way in which the field evolved influenced by institutions and organizations as well as by individuals”.

Volume 4 tells its story in three distinct ways. The Preface by Tom Ban is subdivided into eight areas of enquiry; NIMH programs, Rating Scales, Assessment Instruments, ECDEU Investigators, Other (non-drug) Factors, Atypical Antipsychotics, Therapeutic profiles and Target Populations. The Interviews in alphabetical order were conducted between 1994 and 2007 by ten colleagues or peers. Detailed biographies (Dramatis Personae) of the interviewees are provided by Barry Blackwell (Editor of Volumes 7 and 9).

These three sources of information are blended into the following brief summaries of each scientist’s or clinician’s contributions.

Joseph Autry III had an extended but largely unsung leading role in NIMH and ADAMHA Programs for almost a quarter century during which time he developed the Mental Health Clinical Research Program, was Director of the Division of Extramural Research and finally Director of the Office of Policy Analysis and Co-ordination.

Ten of the interviewees (a third) were involved in the development of Rating Scales. Cole was a genial, much beloved, member of the ACNP (President 1996) who made a pioneer contribution in the earliest years as the first Chief of the NIMH Psychopharmacology Research Center (1956-1966) where he set up the ECDEU program. Later, as Superintendent of Boston State Hospital and Professor of Psychiatry at Tuft’s Medical School (1967-1976) he oversaw the process of de-institutianolization. His lifetime academic output was prolific; he published over 180 scientific articles, 63 book chapters and 12 books, remained a consultant to NIMH throughout his career and was managing editor of Psychopharmacology for over a quarter century. Gardos was mentored by Cole and devoted much of his career to the study of tardive dyskinesia including its etiology, natural history and clinical features, collaborating with

Simpson to develop a rating scale for its manifestations. Klett, a founding member of the ACNP, spent his career at the Veteran's Administration where he was involved in the earliest multicenter clinical trials of major tranquilizers. He pioneered the development of many different rating scales the best known of which are the Inpatient Multidimensional Psychiatric Scale (IMPS) with Lorr and the Nurses Observational Scale for Inpatient Evaluation (NOSIE) with Honingfeld. During his 30- year career at Perry Point VA he fulfilled major administrative roles and served on review committees or assistant to the NIMH, FDA, NIDA, NIH and WHO. Levine succeeded Cole as Director of the Psychopharmacology Research Center where he collaborated with Schooler to develop the Abnormal Involuntary Movement Scale (AIMS) to rate the severity of tardive dyskinesia. "Jerry" completed a twenty year stint at the NIMH including as chief of the Pharmacologic and Somatic Treatments Research Branch (1967-1984) during which time he ran the ECDEU program, a cornerstone for clinical research independent of the pharmaceutical industry and a seedbed for standardized rating scales and data analysis still in use today. McNair obtained his Ph.D. in 1954 at the dawn of psychopharmacology and worked in VA settings with Lorr and Hollister on the first multi-center trials. Doug and his colleagues developed the Profile of Mood States (POMS) and its manual through several revisions, making major contributions to trial methodology. Overall was a psychologist with a special interest in statistics who joined the VA in 1959 as Chief of Criterion Development at Perry point where he worked with Gorham to develop the Brief Psychiatric Rating Scale (BPRS). Over a 40 year career he interacted with the leading scientists in neuropsychopharmacology and was consultant or board member to the ECDEU, ACNP, CINP, VA, NIMH and WHO. Raskin was also among the talented psychologists who developed research designs and rating scales for the pioneer VA multi-center studies. He served as Chief of the Anxiety Disorders Section at the NIMH (1964-1986) during which time he developed the Raskin Rating Scale to measure changes in drug treatment of depression. Allen prided himself on having worked in every area of psychopathology, an ACNP member from 1970 he consulted to the FDA, VA and ADAMHA. Schooler earned her Ph.D. on the language patterns in schizophrenia working with Goldberg on the first NIMH 9 hospital collaborative study of chlorpromazine and placebo. As a clinician and academic she helped design and co-ordinate drug studies on schizophrenia that set benchmarks for clinical practice and, in collaboration with Hogarty and Weismann, she developed a Social Adjustment Scale (SAS II). Nina was among the first women elected to the ACNP (1975) and a member of 8 of its

committees over 30-years. Her scientific publications and teaching activities were prolific, covering every part of schizophrenia treatment and outcome. Simpson began his long and iconic career at Rockland State Hospital with Nate Klein where he was an early ECDEU investigator working with Sugarman and Gallant on every anti-psychotic as it came on the market. Among his major accomplishments was the development of the Simpson-Angus Extrapyramidal Effects Scale (ESRS). George became an early member of ACNP in 1965 and served as President in 1991. Vinar's career is entwined with the history of dual cultures, the Czechs and Slovenes, within which he spent a remarkably productive career under adverse circumstances. Trained in Pavlovian psychiatry he graduated to the earliest psychotropic drugs and by 1958 had developed controlled clinical trials and designed rating scales for psychotic and depressive symptoms (FKP and FKD) launching multi-center studies as early as 1961 –the year ACNP was founded. Even under a Communist regime and stringent economic constraints he was able to amass data on hundreds of patients with schizophrenia and depression with the ability to correlate receptor affinities with effects on symptoms independent of nosology.

Four clinicians were involved in the development of broad based Assessment Instruments. Blackwell's diverse career transcends our categories. As a psychiatry resident he was involved in the discovery, animal and clinical research on the interaction between MAO Inhibitors and amine containing foods. During a subsequent brief spell as a family doctor he worked with Goldberg to develop the General Health Questionnaire (GHQ) an early instrument designed to detect psychiatric disorders in primary care. After immigrating to America and returning to psychiatry and pharmacology he became interested in non-drug factors (placebo response and compliance). He also collaborated with Ayd as co-editor of "Discoveries in Biological Psychiatry" which recorded the verbatim accounts by the scientists and clinicians who discovered and worked on the earliest psychotropic drugs. Katz entered the field of psychopharmacology with degrees in chemistry and psychology at ground zero. He was recruited by Cole to be Executive Secretary of the first Psychopharmacology Research Center at NIH. Reverting to active research he developed the Katz Adjustment Scales for measuring clinical and social adjustment. In a long career devoted to diverse interests Marty developed an NIMH lab to study the early psychedelic drugs and later evaluated the influence of culture on schizophrenia. In 1968 he became director of the Clinical Research Branch at NIMH exerting a profound influence on the development of the field and creating a seedbed for training outstanding

researchers. Late in his career Katz developed the Video Interview Behavior Evaluation Scales (VIBES) and he is the editor of Volume 10 in the OHP series on the history of the ACNP of which he was Vice-President in 1978. Lecrubier's creative and prolific career in France included Director of Research at the world-renowned Saltpetriere Hospital and his lifelong body of research included a 15-minute structured interview (MINI) which yields a DSM IV and ICD-10 diagnosis, translated into 45 languages. Yves identified retardation as the key biological feature of major depression and he contributed to the WHO study of psychological problems in primary care involving 26,000 patients in 15 countries. Paykel trained as a physician in New Zealand, as a psychiatrist at the Maudsley Hospital in London and conducted research in America and Britain that earned him an international reputation in the biological, social and psychological understanding of depression. From 1967 to 1971 he worked with Klerman at Yale first on a cluster analysis that identified subtypes of depression and then on an epidemiological study of over 900 subjects using a scale that established a relationship between life events and the onset of depression (Life Events Scale). In addition to Simpson (see under Rating Scales) three other clinicians were Early Clinical Drug Evaluation Unit Investigators who played a pivotal role in the evolving art and science of clinical trials that identified and established the first generation of psychotropic drugs deemed safe and effective. Ban, series editor of the OHP, is another iconic figure. No living psychiatrist has a comparable scientific, conceptual, historical and international grasp of the breadth and depth of our field. Working originally with Lehman Tom helped characterize several phenothiazines, butyrophenones, thioxanthines and tricyclic antidepressants. His contributions and publications are prolific; he has authored or edited over 50 books and 700 articles. Tom is the recipient of numerous awards and member of many national and international organizations. Gallant is a Renaissance man in every meaning of that word. Working with Bob Heath at Tulane University on subcortical electrodes in schizophrenia he was also Co-Principal Investigator of one of the first ECDEU programs working with Mel Bishop and testing the first psychotropic drugs on in and outpatient populations that yielded 35 publications in three years (1963-1965), contributing to Don's induction to the ACNP in 1963. His lifetime bibliography lists 230 publications, including 36 book chapters and 9 books. Goldstein was a pharmacist before becoming a psychiatrist and spent his entire career at the University of Miami with professorships in Psychiatry, Pharmacology, Epidemiology and Public Health. Burt did research on several of the early major tranquilizers and antidepressants for the

ECDEU and was the first investigator with Brauzer to use “symptomatic volunteers” in drug trials.

Several pioneers were interested in “Non Drug” Factors. In addition to Schooler (see Rating Scales) and Blackwell (see Assessment Instruments) two others made seminal contributions. Rickels has had a long and productive research career, extending into his eighties. It began in 1957 when he became involved in the NIMH Psychopharmacology Center with Uhlenhuth, Covi and Lipman, joining the CINP in 1958 and ACNP in 1961. Karl retained his earlier interest in psychoanalysis to investigate the psychosocial factors influencing drug outcomes leading to his first book, “Non-Specific factors in Drug Therapy” (1968). Much of his early research also included anti-anxiety agents about which he espouses a moderate philosophy. Later work involved the interface between psychiatry, obstetrics and gynecology with a named Professorship in Human Behavior and Reproduction. Hogarty had a unique career trajectory. Holding a Master’s degree in Social work he is one of the few members of ACNP without a doctoral degree preferring “privately acquired” knowledge in a variety of disciplines that enabled him to study the psychosocial factors (“add ons”) that influence outcome of drug treatment in schizophrenia. As Principal Investigator in the first NIMH funded long term study of this issue he developed Major Role Therapy (MRT) to address the problem of “expressed emotion” using family “psychoeducation” to reduce relapse rates. What followed was a small group approach designed to improve social skills called Cognitive Enhancement Therapy (CET).

Two interviewees have contributed research on Atypical Antipsychotics (so called “second generation” drugs). Kane was mentored by Don Klein and became Director of Psychopharmacology Research at Hillside Hospital the year after he graduated in psychiatry (1976). He remained in this setting for almost 40 years and focused his research primarily on every aspect of schizophrenia producing a body of knowledge that includes over 200 articles, 30 book chapters and 5 books. Of particular interest was research on Clozapine, the first of the atypical antipsychotics with its unique clinical characteristics. Lieberman collaborated with Kane early on and became Principal Investigator in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a multicenter NIMH 60 million dollar study which demonstrated that “atypical” neuroleptics had a different side effect profile but offered no advantages over first generation drugs in efficacy or therapeutic profile. Lieberman was a latecomer to the ACNP

(1989) but has been active in the organization as well as in the APA, NIMH, DSM IV, FDA and Society of Biological Psychiatry (President 2005).

Five interviewees have been active in defining the Therapeutic Profile of drugs available in clinical practice. Bowden began his long and distinguished career under Spitzer and Endicott studying methadone in opiate addiction. Aware of its “prophylactic” maintenance properties at a time when bipolar disorder was often mistaken for schizophrenia but lithium was poorly tolerated he began a large scale study of valproate as an alternative, leading to FDA approval in 1995 followed by co-editing the book, “Bipolar Medication: Mechanism of Action” (APA Press 2000). Dr.Bowden’s commitment to patient care was reflected in advisory roles to the advocacy organizations, NDMDA and NAMI from both of which he received named awards. Uhlenhuth worked at the threshold of psychopharmacology on comparisons between meprobamate, phenobarbital and placebo when drugs were considered “adjunctive” to psychodynamic therapy. This began a distinguished career establishing the efficacy of drugs in schizophrenia, depression, panic disorder and bereavement. “Uhli’s" interests covered a broad spectrum including early work on non-drug factors and later, at NIMH with Mitchell Balter, on the interaction of pharmacologic and psychosocial factors as well as the epidemiologic study of experts ‘opinions on psychotropic drugs including benzodiazepines. Kocsis can be considered a “second generation” psychopharmacologist who completed training in 1975 and became a member of ACNP in 1987. Jim devoted himself to studying the etiology, nosology and natural history of the DSM III category “Depressive Dysthymia”. In doing so he demonstrated the efficacy of tricyclic and SSRI antidepressants on social function in the disorder. A. Winokur’s interest in psychopharmacology was inspired by summer electives in Shildkraut’s lab at Mass Mental Health Center and eventually led to joining an increasing number of ACNP members with both a Ph.D. and M.D degree. This resulted in research on the distribution of thyrotropine stimulating hormone (TSH) in rat brain and its translational application in enhancing the effect of antidepressant treatment in major depression. Jim spent a productive career in clinical work, research and education in both psychiatry and pharmacology where he is highly regarded as a teacher of residents and medical students. David Wheatley’s contribution in the development of psychopharmacology was unique, dictated by his role as the only family practitioner. He was 45 in 1960 when psychotropic drugs began to have an impact on his area of practice. David developed a consortium of 500 family physicians from all over Britain and organized them into a

collaborative research group. Due partly to relative disinterest among American primary care physicians in this new field Wheatley's group became the only ECDEU research center outside of North America and was funded for 12-years. This pioneering work helped characterize the response of milder forms of psychopathology to antidepressants, hypnotics and anxiolytics in primary care.

A final area of study described in Volume 4 is Target Populations. Although early hopes for specificity in treatment outcomes for diagnostic entities have been largely disappointed three investigators made positive contributions. Don Klein pioneered his technique of "pharmacologic dissection" in efforts to link diagnosis with treatment specificity. This included early work on MAO Inhibitors and "atypical depression" and original sustained research on the discovery, diagnosis, neurophysiology and treatment of panic disorder and agoraphobia. Don enjoyed over 40 years of sustained support from NIMH as a Principal Investigator (1964 -2006) and is widely regarded as one of the best critical and creative scientists in the field, the recipient of many awards and a consultant to NIMH, NIAAA, VA, NIH, FDA, and APA. Quitkin, a disciple and collaborator with Don Klein, confirmed and described the clinical features of "atypical depression" and its preferential response to MAOI over tricyclic antidepressants. He also teased apart the distinctive features of drug from placebo responses. Schatzberg, also a "second generation" psychopharmacologist joined the ACNP in 1983 and has played a major role in its governance including as President (2000). During a 36-year span he authored 700 publications and 17 books describing four major areas of research in depression much of it funded by NIMH. This involves biogenic amine metabolism, Hypothalamic-Pituitary-Adrenal Axis dysfunction, psychopharmacologic treatments and the nosology of depression. This body of work has generated international recognition and garnered many distinguished awards.

Documenting the major accomplishments of these 30 scientists and clinicians in discrete areas and short biographies pays scant tribute to their entire careers, described fully in Volume 4.

VOLUME FOUR: INTERVIEWEES AND INTERVIEWERS

Joseph Autry III interviewed by Leo E. Hollister

Thomas A. Ban interviewed by Leo E. Hollister

Barry Blackwell interviewed by Donald S. Robinson

Charles L. Bowden interviewed by Andrea Tone

Jonathan O. Cole interviewed by Leo E. Hollister

Donald M. Gallant interviewed by Thomas A. Ban

George Gardos interviewed by Thomas A. Ban

Burton J. Goldstein interviewed by Thomas A. Ban

Gerard E. Hogarty interviewed by Andrea Tone

John M. Kane interviewed by Thomas A. Ban

Martin M. Katz interviewed by Jean Endicott

Donald F. Klein interviewed by Leo E. Hollister

James C. Klett interviewed by Leo E. Hollister

James H. Kocsis interviewed by Joel Braslow

Yves Lecrubier interviewed by Andrea Tone

Jerome Levine interviewed by Samuel Gershon

Jeffrey A. Lieberman interviewed by Shitij Kapur

Douglas M. McNair interviewed by Leo E. Hollister

John E. Overall interviewed by Thomas A. Ban

Eugene S. Paykel interviewed by Tomas A. Ban

Frederic Quitkin interviewed by Thomas A. Ban

Allen Raskin interviewed by Leo E. Hollister

Karl Rickels interviewed by David Healy

Alan F. Schatzberg interviewed by Thomas A. Ban

Nina R. Schooler interviewed by Thomas A. Ban

George M. Simpson interviewed by Leo E. Hollister

Eberhard E. Uhlenhuth interviewed by Jerome Levine

Oldrich Vinar interviewed by Leo E. Hollister

David Wheatley interviewed by Leo E. Hollister

Andrew Winokur interviewed by Andrea Tone

Chapter 5

Volume 5

NEUROPSYCHOPHARMACOLOGY

Samuel Gershon

Since the birth of neuropsychopharmacology in the 1950s half a century passed and in this volume, the fifth in a ten volumes series, 30 interviewees reflect on their contributions to the development of the field. All 30 interviewees are psychiatrists and members of the American College of Neuropsychopharmacology (ACNP). One of the inetrviewees (Arnold Friedhoff) is founder and past president; and four interviewees, William Bunney, William Carpenter, Herbert Meltzer and Arthur Prange are past presidents of the College.

The thirty interviews were conducted by 15 interviewers in a period from 1995 to 2007 and with the exception of one interviewee, Claude de Montigny, who was interviewed at the biennial congress of he Collegium International Neuro-Psychopharmacologicum (CINP), all interviews were done at annual meetings of ACNP. .

The first fifty years in the history of neuropsychopharmacology was a major turning point for the discipline of psychiatry. The change was dramatic in perspective. It shifted from a general view of therapeutic nihilism to a belief, held by some, that every psychiatric disorder would be accessible to therapeutic pharmacological intervention. It would appear from the lay media, including television that a little bit of “this” drug would help one, or a little bit of “that” drug would help another patient. This was to the extent that psychopharmacological over medication and inappropriate usage of psychotropic drugs has become topics for comedians.

In the following some information on the thirty clinicians and scientists and on their contributions to the development of the field are briefly reviewed:

Burton Angrist graduated with MD from Albert Einstein College of Medicine in 1962 and completed his psychiatric residency at Hillside Hospital in New York in 1966. He moved

then went to New York University School of Medicine (NYU) in 1966 as a research fellow in the Psychopharmacology Research Unit. Burt became a full professor at NYU in 1980.

Burt's research was extensive in scope but his main interests were studies in schizophrenia and the role of dopamine in its pathogenesis. He pioneered a series of studies with amphetamines and related substances and demonstrated that amphetamine could induce a model psychosis of schizophrenia. The clinical condition induced was not just an overactive state but showed the negative syndrome of schizophrenia as well. This chemically induced model could be terminated with any of the dopamine blocker antipsychotics. Angrist's findings were groundbreaking and remain a major building block for the field.

Burt was a dedicated teacher. He also demonstrated remarkable clinical skills.

Burt Angrist is now retired but participates in scientific meetings. He is a Life Fellow of ACNP and a Fellow of CINP.

Ross J. Baldessarini, obtained his MD from Johns Hopkins University in 1963 and completed his psychiatric residency there in 1969. He became Professor of Psychiatry at Harvard Medical School in 1978 and has contributed to psychopharmacology greatly through his many publications, lectures and mentoring of investigators in the US and from around the world. He is an Emeritus Fellow of ACNP.

*Robert Henry (Haim) B*elmaker graduated from Harvard College in 1967 and received his MD from Duke University Medical School in 1971. Bob did his psychiatric residency also there. From Duke he became a Clinical Associate to the National Institute of Mental Health (NIMH).

Bob immigrated to Israel and was Research Director of the Jerusalem Mental Health Center from 1974 to 1985. In 1986, he became Professor of Psychiatry at Ben-Gurion University in Beer Sheva. In both positions in Israel he contributed greatly to the development of biological psychiatry. He is a dedicated teacher and mentor to many young investigators who have attained independent scientific stature.

Belmaker's publications and scientific work cover a broad spectrum including clinical and basic neuroscience research.

He was President of CINP from 2008 to 2010 and is a Foreign Corresponding Fellow of ACNP.

Walter A. Brown graduated from Duke University with an MD in 1967 and completed his psychiatric residency at Yale in 1972. He became Clinical Professor of Psychiatry at Brown University in 1994 and retains that position to date. .

Walter set up a group to conduct clinical trails that developed into Clinical Research Centers International. The organization was formally established in 2000 with Brown as its president.

Brown has published extensively on findings in clinical trials with a variety of psychotropic agents.

He is a Member of ACNP

William E. Bunney Jr. has had a celebrated career as a scientist and administrator. He obtained his MD in1956 from the University of Pennsylvania Medical School and completed his residency in psychiatry at Yale in 1960.

From 1960 to 1982 Bunney played a major role in a number of research programs at NIMH in both senior administrative and research positions, involving affective disorders and many new research areas. He accepted the position of Chairman of Psychiatry at the University of California at Irvine in 1982. He has remained active in research and is currently Co-Chairman of the Department.

Bunney was President of ACNP in 1983 and of CINP from 1986 to1988.

William T Carpenter Jr. has been a major figure in Schizophrenia research for most of his career.

He was a research psychiatrist at NIMH from 1966 to 1975 and in1977 he became Director of the Maryland Psychiatric Research Center and Professor of Psychiatry at the University of Maryland. He continues in these positions and is still actively engaged as a productive scientist and administrator.

Carpenter was President of ACNP in 2007.

Bernard J. Carroll, went to medical school in Melbourne, Australia. He graduated with a BSc degree in pharmacology 1961 and received his MD in 1964. He also completed his psychiatric training in Melbourne in 1969 with a DPM (Diploma in Psychological Medicine) and a PhD in Psychobiology in 1971. During his training he acquired a solid background in the basic neurosciences.

In 1971 moved from Australia to the United States and joined the Department of Psychiatry, University of Pennsylvania, as a research fellow. He stayed in the department for another year as Assistant Professor before moving to the Department of Psychiatry, University of Michigan, in 1973 as an Associate Professor to become full Professor in1976. In 1983 Carroll was appointed Chairman of the Department of Psychiatry at Duke University in Durham, North Carolina.

Carroll has been active in research, primarily in affective disorders. He used psychoendocrinology, primarily the dexamethasone suppression test to identify different types of depression. His research produced a major impact on understanding the nosology and etiology of these disorders.

Carroll is an Emeritus Fellow of ACNP.

Guy Chouinard, received his MD from the University of Montreal in 1968. He had intensive training in psychiatry and pharmacology. He was appointed Professor of Psychiatry at the University of Montreal in 1987 and McGill University in 1990.

Chouinard has been a prolific research investigator in neuropsychopharmacology. In schizophrenia he contributed to the understanding of its pathophysiology. He studied the mode of action and side effects of neuroleptic drugs. His contributions are diverse and extensive. They have had a major impact on treatment practices.

Chouinard is a Member of ACNP and a Fellow of CINP.

John M. Davis was born in Kansas City, Missouri in 1933 and did his undergraduate work at Princeton in creative writing, He went to medical school at Yale, graduating in 1960 and

completed his psychiatric residency at the Massachusetts General Hospital in 1964 at a time when the dominant theoretical structure for psychiatric training was psychoanalytic. From there he went to NIMH to work with William Bunney on the biochemistry of depression.

John Davis and Joseph Schildkraut published the key papers on the role of biogenic amines in depression separately and independently, but at about the same time. John became interested in lithium in the 1960s and began treating the first patients with lithium after a lecture at NIMH by Sam Gershon.

In 1969 John Davis and Donald Klein published a comprehensive textbook on psychopharmacology that became a standard reference at the time.

After John left NIMH went to work at Vanderbilt and together with David Janowsky he published interesting clinical experiments using physostigmine to study the role of acetylcholine in depression.

From Vanderbilt John Davis went to the Illinois State Psychiatric Institute as the Director of Research.

Davis has been very active and productive scientifically and has published numerous scientific papers and books.

He is a Fellow of ACNP and CINP.

Claude de Montigny received his MD in 1968 and his PhD in 1974 from the University of Montreal. From 1976 to 1977 he spent a fellowship in I neurophysiology with George Aghajanian at Yale and while still there started some of his most important neurophysiologic studies.

De Montigny became Professor of Psychiatry in 1985 at the University of Montreal and in 1987 at McGill. His scientific work continued in many areas of neurophysiology and he contributed immensely to understanding of the role of serotonin in the action of antidepressants.

De Montigny is Emeritus Member of ACNP and Past President (1996 to 1998) of CINP..

Jan A. Fawcett graduated from Yale in 1960 as an MD. He had his psychiatric residency training at Langley Porter Institute at the University of San Francisco and then at the University of Rochester. In 1964 and 1965 he was a Clinical Associate at NIMH and from there he went on to the Illinois State Psychiatric Institute (ISPI) to work with James Maas.

At ISPI he established a major research program on depression and the role of catecholamines in depression. He has been especially interested in suicide and suicidality in various disorders.

In 1972 Fawcett became Professor and Chairman of Psychiatry at Rush Medical College where he continued his research and has become a strong advocate of education and research in depression,

Dr. Fawcett is a Fellow of ACNP.

Arnold J. Friedhoff graduated with an MD from the University of Pennsylvania in 1947 and became Professor of Psychiatry and Director of the Millhauser Laboratories at NYU in 1969. He combined a clear, committed and close interest in clinical research together with studies in basic neuroscience. This permitted him to ask and answer highly clinically relevant questions.

Friedhoff was one of the first people to propose and use L-DOPA as a treatment for

Parkinsonism although the doses he used were too small to show a consistent therapeutic effect. Others continued and demonstrated a clear effect of the substance at a higher dosage.

Friedhoff was also involved in research with the “pink spot,” he identified in the urine of schizophrenics, and assumed to be caused by a toxic substance, but which turned out to be an artifact.

Frederick K Goodwin, a laboratory and clinical researcher, is a truly central figure in psychiatry and psychopharmacology. He joined the NIMH in 1965 and has become an internationally recognized authority on the research and treatment of major depression and manic depressive illness. He and Kay Jamison authored the classic textbook on Manic Depressive Disorder in 1990.

Goodwin made substantial contributions as a senior administrator, Scientific Director and Chief of the Intramural Research Program of NIMH, from 1981 to 1988. Subsequently, he was Director of ADAMHA from 1988 to 1994. Currently, he is Professor of Psychiatry and Director of the Center on Neuroscience, Behavior and Society at the George Washington University Medical Center in Washington, DC.

Goodwin is a recipient of several major research awards including the Hofheimer Prize from APA and the Anna Monika Prize for research in depression. He has authored over 400 publications.

Goodwin is a Fellow of ACNP and CINP

John F. Greden, received his medical degree from the University of Minnesota Medical School, completed an internship at the University of California Los Angeles (UCLA) Harbor General Hospital in Los Angeles, and was a resident in psychiatry at the University of Minnesota hospitals and Walter Reed Army Medical Center. Prior to joining the faculty of the medical school at the University of Michigan, in 1947 he served as Director of Psychiatry Research at Walter Reed. Greden served as Chair of the Department of Psychiatry at the University of Michigan from 1985 to 2007.

Greden's clinical and research activities have emphasized the study of the longitudinal course of depression, linkages between stress hormones and depressive recurrences, and clinical strategies for preventing such recurrences. He was the senior editor of scientific publications for the American College of Neuropsychopharmacology from 1998 to 2001.

Angelos E. Halaris had his early education in Athens, Greece. Then, he went to medical school at the University of Munich and graduated MD, PhD in 1967. He did his residency in psychiatry at the University of Chicago from 1974 to 1977.

In 1984 Halaris became Professor of Psychiatry and Pharmacology and Vice Chairman at Case Western Reserve University. He devoted a major part of his work to studies in depression and bipolar disorders. His work was truly translational in scope.

Hallaris is a Fellow of ACNP and CINP.

David S. Janowsky obtained his MD from the University of California at San Francisco in 1964 and did his psychiatric residency at University of California at Los Angeles from 1956 to 1966. Subsequently he was clinical associate at NIMH, worked with John Davis in the Clinical Division of the Tennessee Neuropsychiatric Institute, and in the Department of Psychiatry of the University of California in San Diego. Janowsky became Chairman and Professor of Psychiatry at the University of North Carolina at Chapel Hill in 1986. He stepped down from the chair in 1994 but stayed at Chapel Hill to conduct research in the Alcoholism Center.

Janowsky published extensively in psychopharmacology including some extremely interesting studies exploring the role of cholinergic systems in bipolar disorder (BD) and the effect of drugs on that system.

Daniel P. van Kammen, was born in the Netherlands and had his early education there. He obtained his MD and PhD in Pharmacology at the University of Utrecht.

He came to the US and did his psychiatric residency at Johns Hopkins Hospital in Baltimore from 1970 to 1973 and then worked at NIMH for five years. In 1982 he moved to the Veterans Administration (VA) Hospital, affiliated with the University of Pittsburgh.

Van Kammen left Pittsburgh in 1998 to join RWJ Pharmaceutical Research Institute in New Jersey. Currently he is Chief Medical Officer of CHDI Foundation, Inc., a private non-profit organization working on Huntington's disease.

During his professional career van Kammen was involved in research on schizophrenia, bipolar disorder and post-traumatic stress disorder.

He published extensively and was a widely sought after lecturer.

Shitij Kapur obtained his medical degree from the All India Institute of Medical Sciences in New Delhi and then came to Pittsburgh (USA) and Toronto (Canada) to complete his psychiatric residency. He obtained his PhD. at the University of Toronto in 1996.

Kapur carried out research on receptor function employing many different techniques including positron emission tomography (PET) in schizophrenia and Alzheimer's' Disease. He

also studied the mode of action of antipsychotic agents for many years and has made immense contributions in many areas of neuropsychopharmacology

Kapur is a member of ACNP and a Fellow of CINP.

Alfred J. Lewy obtained his MD, PhD from the University of Chicago in 1973 and was at NIMH from 1975 to 1981. He then went to work at the University of Oregon in Portland in Pharmacology and Ophthalmology.

Lewy's research over many years involved control systems in circadian cycles and especially the role of melatonin and the connections between circadian rhythms, mental illness and sleep disorders.

Lewy is a Fellow of ACNP.

Herbert Y. Meltzer has been an outstanding figure in psychopharmacology and an established scientist in the field. He obtained his MD at Yale in 1963 and was Professor of Psychiatry at the University of Chicago from 1974 to 1985. In 1985 he moved to Case Western Reserve University with an appointment in the Medical School in Psychiatry and Pharmacology. From case Western, in 1996, he moved on to Vanderbilt University as Professor of Psychiatry.

Meltzer's research into all aspects of schizophrenia and the mode of action of antipsychotics has established him as a major contributor in his field of expertise.

Meltzer was President of ACNP in 1985 and of CINP from 2002 to 2004.

Gregory F. Oxenkrug obtained his early training in Leningrad, Russia (Soviet Union). His was a co-worker of Izyastlav Lapin. The work of Oxenkrug and Lapin was an early forerunner in proposing the major role of serotonin in the action of antidepressant drugs.

In 1980 Oxenkrug came to the US as an Associate Professor of Psychiatry at Boston University. In 1982 he moved to become Associate Professor of Psychiatry at Wayne State University and worked at the Lafayette Research Clinic in Detroit.

Oxenrug's scientific work has included studies on the psychopharmacology of the pineal gland. He studied the role of its hormone, melatonin, in psychiatric conditions.

He is now a Professor of Psychiatry at Tufts University and very active in his scientific pursuits.

Oxenkrug is an Emeritus fellow of ACNP.

Robert M. Post is an internationally recognized expert on bipolar disorder and has published and lectured extensively on related topics around the world.

Post obtained his MD in 1968 from the University of Pennsylvania and completed his psychiatric residency at Massachusetts General Hospital in Boston in 1970. He then went to NIMH and in 1981 was appointed Chief, Biological Research Branch. He has recently retired from that position but continues to write and lecture widely and is contributing to discussions on bipolar disorder to the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Asssociation in preparation.

Post is a Fellow of ACNP and CINP.

William Z. Potter received his MD in 1970 and PhD in 1972, both from Indiana University. He is trained in both psychiatry and pharmacology.

From 1971 to 1974 Potter was a Research Associate in Pharmacology and Toxicology at the National Institutes of Health (NIH). After completing residency training in psychiatry in 1976 at NIMH, he continued on the staff of the Intramural Program till 1988.

Potter's initial work at NIH was in drug metabolism in the course of which he became keenly interested in psychiatric drugs. Together with Dred Goodwin, he carried out a number of projects on the biology of affective illness.

Potter has published approximately 300 scientific papers. After leaving NIMH he joined industry and worked first at Eli Lilly and is currently at Merck.

Potter is a Fellow of ACNP and CINP.

Herman M. van Praag obtained his MD in 1956 from the State University, Leiden, the Netherlands and his PhD. degree in Neurobiology from the University of Utrecht.

He became Professor of Psychiatry at the University of Groningen in 1970 and Professor and Chairman, Department of Psychiatry at Albert Einstein College of Medicine in New York in 1982. In 1992 he returned to Maastricht University in The Netherlands as Professor and Chairman of the Department of Psychiatry. He retired from that position in 1997.

Van Praag published extensively on the biological aspects of schizophrenia and affective disorder as well as the mode of action of psychiatric drugs. He is the recipient of many honorific awards, including the CINP Pioneer Award.

Van Praag is Emeritus Fellow of ACNP.

Arthur J. Prange Jr. obtained his MD from the University of Michigan in 1950 and completed his psychiatric residency in 1957 at the University of North Carolina at Chapel Hill. He became the Boshamer Professor of Psychiatry at Chapel Hill in 1983.

Prange's area of research interest was Psychoendocrinology. He was especially interested in the role of the thyroid in affective disorders. His contributions to this theme have influenced current interest in using thyroid preparations to augment treatment effects in depression.

Prange was President of ACNP in 1987.

Elliot Richelson received his MD from the Johns Hopkins University School of Medicine in 1969 and continued with his residency and research training there till 1975.

In 1975 Richelson joined the Mayo Clinic as an assistant professor. He became Director for Research at the Mayo Clinic in Jacksonville, Florida and has been involved in basic and clinical research in psychopharmacology.

In 1977 Dr. Richelson received the A.E. Bennett Basic Science Research Award of the Society of Biological Psychiatry and in 1985 the Daniel Efron Award of the ACNP.

Richelson is Fellow of ACNP and CINP.

Donald S. Robinson, graduated MD from the University of Pennsylvania in 1959 and obtained an MS in Pharmacology from the University of Vermont in 1966. He trained in Internal Medicine in Burlington, Vermont from 1960 to1965.

Robinson became Professor and Chairman, Departments of Pharmacology and Professor of Psychiatry and Medicine in 1977 at the University of Vermont. His primary area of research interest was in the relationship between monoamine oxidase (MAO) inhibition and antidepressant effects. In 1984 Robinson left academic psychiatry and joined Bristol-Myers Squibb in Connecticut as Vice-President for Clinical Research where he was involved in a number of drug studies with agents such as a gepirone, buspirone and trazodone.

Robinson is Emeritus Fellow of ACNP.

Joseph J. Schildkraut, had a special reputation in psychopharmacology. He was a protagonist and crusader for the role of catecholamines in the pathogenesis of depression. Schildkraut obtained his MD from Harvard Medical School in 1959 and completed his residency in Psychiatry at the Massachusetts Mental Health Center in Boston. After residency he spent five years, from 1963 to 1968 at NIMH. From NIMH, he returned to Harvard Medical School and became a full Professor of Psychiatry in 1974.

Schildkraut was a co-awardee of the Anna Monika Foundation Prize in 1967 for his work on norepinephrine metabolism in depression.

He retired from Harvard due to ill health, developed a major interest in paintings and became an art expert.

He was Fellow of ACNP and CINP.

Baron Shopsin was born in New York and had his early education there, graduating as a Far Eastern History major from Brooklyn College. He went to medical school in Belgium and after returning to the United States did a residency in psychiatry at Cornell and New York University School of Medicine.

Shopsin was involved in early research with lithium in the United States. His studies with MAO inhibitors contributed to the identification of the possible cause of antidepressant action. After his stint in research Shopsin served as consultant to the pharmaceutical industry and was involved in developing psychotropic drugs.

Peter Charles Whybrow had his original education in England and received his MD in London from the University College Hospital Medical School in 1962.

He came to the US in 1965 as a Resident in Psychiatry at the University of North Carolina. In 1969 he took the position of Assistant Professor of Psychiatry at the Dartmouth Medical School in New Hampshire and in 1971 became Professor and Chairman there. In 1984 he was appointed Chairman of the Department of Psychiatry at the University of Pennsylvania School of Medicine in Philadelphia. He is currently the Chair of Psychiatry at University of California at Los Angeles School of Medicine.

Whybrow has been active in teaching and research where he has been a leading figure in exploring the role of thyroid function in depression and its treatment.

Whybrow is member of ACNP and a Fellow of CINP. .

Interviewees included in Volume Five entered the field at different stages in the development in neuropsychopharmcology. Hence the transcripts cover fifty years of history including the generation of hypotheses about the pathophysiology of depression, the mode of action of tricyclic antidepressants, the generation of hypotheses about the pathophysiology of bipolar disorder and the mode of action of anticonvulsants.

The content of the volume is connected to the content of the volumes that precede and follow it by Tom Ban, the editor of the series. It is dedicated to the memory of Leo E. Hollister, a pioneer of neuropsychopharmacology.

VOLUME FIVE: INTERVIEWEES AND INTERVIEWERS

Burton Angrist interviewed by David S. Janowsky

Ross J. Baldessarini interviewed by David Healy

Robert H. Belmaker interviewed by Joseph R. Calabrese

Walter A. Brown interviewed by John F. Greden

William E. Bunney, Jr. interviewed by Thomas A. Ban

William T. Carpenter Jr. interviewed by Thomas A. Ban

Bernard J. Carroll interviewed by Leo E. Hollister & Thomas A. Ban

Guy Chouinard interviewed by Andrea Tone

John M. Davis interviewed by David Healy

Claude de Montigny interviewed by Andrea Tone

Jan A. Fawcett interviewed by Frederick K. Goodwin

Arnold J. Friedhoff interviewed by Benjamin S. Bunney

Frederick K. Goodwin interviewed by Thomas Detre

John F. Greden interviewed by Thomas A. Ban

Angelos E. Halaris interviewed by Leo E. Hollister

David S. Janowsky interviewed by Leo E. Hollister

Shitij Kapur interviewed by Elizabeth Bromley

Alfred J. Lewy interviewed by John M. Davis

Herbert Y. Meltzer interviewed by Stephen H. Koslow

Gregory F. Oxenkrug interviewed by Thomas A. Ban

Robert M. Post interviewed by Thomas A. Ban

William Z. Potter interviewed by Thomas A. Ban

Arthur J. Prange interviewed by Robert H. Belmaker

Elliott Richelson interviewed by Thomas A. Ban

Donald S. Robinson interviewed by Joel Braslow

Joseph J. Schildkraut interviewed by David Healy

Baron Shopsin interviewed by Andrea Tone

Daniel P. van Kammen interviewed by Thomas A. Ban

Herman M. van Praag interviewed by David Healy

Peter Whybrow interviewed by Andrea Tone

Chapter 6

Volume 6

ADDICTION

Herbert D. Kleber

In the first five volumes of this series the focus is on different methodologies used to study psychotropic drugs. In Volume Six the focus shifts to the employment of these methodologies in the study of addiction. It deals with interviewees' contributions to the biological underpinnings of addiction, and to the development of rational pharmacological treatments for addiction.

At the beginning of the 20th century, addiction was commonly viewed as synonymous with physical dependence and withdrawal. Treating opiate withdrawal symptoms was viewed as treating addiction. Relapse was clear evidence of moral failure. However, relapse was so common that clinics were opened where maintenance heroin or morphine were given. These were shut down in the early 1920's because of diversion and failure to lead to abstinence. Given the short acting nature of the maintenance drugs, patients had to either return to the clinic 2-3 times a day, making holding a job difficult, or were given take-home doses that led to diversion. Over the next decades, approximately 25,000 physicians were indicted and as many as 10% were imprisoned for prescribing maintenance narcotics to addicts.

In 1935, the U.S. Public Health Service Prison/Hospital opened in Lexington, KY. This was a unique facility in a number of ways. It was both a Federal prison for treating addicts and a hospital where "volunteer" addicts could get treatment. The "volunteers" were individuals under pressure to go to Lexington such as doctors and nurses whose licenses were at stake. Their usual length of stay was 6 months whereas the prisoners were doing 1-10 years. It was also co-ed with a separate wing for women. There were 1000 individuals overall and the buildings were on 1000 acres. The Addiction Research Center (ARC) was also there, the National Academy of Science's attempt to develop an addiction science out of which pharmacologic treatments would emerge.

During the 40 years before ARC became the intramural arm of NIDA in Baltimore, in the 1970's, it laid the groundwork for our current knowledge of addiction

One of the ARC's goals was to find a "non-addicting narcotic" which led to studies of other drugs. These included methadone, naltrexone and cyclazocine a mixed agonist/antagonist, as well as THC and hallucinogens. A number of the scientists in volume 6 spent time at Lexington (e.g. Jaffe, Jasinski, Kleber, Kornetsky) and others were influenced by the work there. A number of scientists in Volume 6 have received the Eddy Award, the highest scientific award from CPDD (College on Problems of Drug Dependence). These include: Adler, Jaffe, Kleber, Kornetsky, Kreek, O'Brien, Schuster, Way, and Woods.

Dr. Jerome Jaffe tells how he came across Wikler's work and decided to go to Lexington to study with him. He later went to the University of Chicago and founded a multimodality program in 1968. He was among the 1st to study LAAM. He than went to Washington as the head of SAODAP (Special Action Office for Drug Abuse Prevention) under President Nixon, and he used the President's concern over the returning Vietnam veterans, many of whom had become addicted to heroin while there to get Nixon committed to expanding Methadone Maintenance. The President wanted to be seen as a "law and order" President and was afraid that the returning vets could trigger a crime wave. Jaffe was the 1st "Drug Czar" and later became director of the ARC in the '80's after it had moved to Baltimore. Prior to that he had focused on nicotine as an addiction while at the University of Connecticut.

Dr. Donald Jasinski went to Lexington in 1965 and working with Bill Martin there, helped develop the idea of "protracted abstinence." Major work on naltrexone for opiate dependence (early '70's) was done by Jasinski both at ARC and later at Johns Hopkins. He also was one of the 1st to study buprenorphine as a maintenance agent, with now over 325,000 currently maintained.

Dr. Conan Kornetsky spent 4 years at the ARC and demonstrated the importance of morphine's effect on anxiety and its relation to morphine's analgesic effect. His work with drugs and brain stimulation demonstrated the role of the reward system in drug dependence, providing evidence that dopamine was a common substrate for the rewarding effects of cocaine and morphine.

After 2 years at Lexington while in the Public Health Service, Dr. Herbert Kleber became concerned about it's very high relapse rate and when he returned to Yale in 1966 decided to focus on improving addiction treatment. At Yale he developed a model NIH funded multimodality treatment and research program in 1968, one of the 1st in the country. He was involved in the dissemination and longterm safety of M.M., early research on naltrexone, and early research on buprenorphine. He was also involved in early attempts to develop medications for cocaine and later for marijuana dependence. An early finding with Mark Gold was clonidine for opiate W/D, the 1st non-opiate to ease opiate W/D and made possible rapid opiate W/D via antagonists. From 1989-91 he was the Demand Deputy at ONDCP (Office of National Drug Control Policy) under "Drug Czar" William Bennett and the 1st President Bush. He than left Washington and went to Columbia University in 1992 where, collaborating with his wife the late Dr. Marian Fischman, he began the Substance Abuse Treatment Unit modeled on what he had done at Yale. Both the Yale and the Columbia programs are considered leaders in the field.

One of the earliest treatment payoffs for the groundbreaking work at Lexington was the development of methadone maintenance at the Rockefeller Institute in the mid 1960's. The pioneering work of Dole and Nyswander, with the assistance of Dr. Mary Jeanne Kreek, led to methadone maintenance, now used in countries around the world. Kreek went on to document the longterm safety of methadone, the role of mu and kappa opioid receptors in responsiveness to stress and in relation to cocaine and alcohol addiction as well. She is involved now with genetic research.

Dr. Martin Adler advanced the ARC work by finding that lesioning different sites in the brain could abolish various signs of withdrawal. He made a number of findings on the importance of endogenous and exogenous opioids on analgesia, thermoregulation, and brain excitability. Most recently he has focused on interaction of chemokines and drugs of abuse that could improve treatment of chronic pain.

Dr. Charles O'Brien founded the University of Pennsylvania VA Addiction Treatment Center, became very interested in Wikler's behavioral research and applied it to human addicts. He demonstrated in human lab studies that craving and withdrawal are conditioned responses with physiological concomitants (1977), one of the earliest demonstrations that addiction was a learned response, with memory persisting long after drugs were gone from the body. He and

Volpicelli conducted the 1st studies of naltrexone for alcohol dependence and later found that individuals with a gene variant of the mu opioid receptor had enhanced naltrexone efficacy.

Dr. Eddie Way, in his research over 30-years, demonstrated that "tolerance" and "dependence" had a common biochemical basis, an increase in norepinephrine release. Dr. Charles Schuster's early work found stimuli associated with morphine injections could temporarily reverse opiate W/D. He developed animal models of self-administration and in collaboration with Fischman and others, he showed a relationship between plasma concentration and the subjective and physiological affects of cocaine. From 1986-92 he was the Director of NIDA where he established the Medication Development Division.

Dr. Roger Meyer had a career that encompassed both heroin addiction and alcoholism. He established a NIDA-funded research program on opiate addiction in Boston in the 70's using human and parallel animal model research. He found that reports of craving were validated by drug self-administration behavior and that craving was rewarding and not aversive. In 1978 he became Chair of Psychiatry at the Univ. of Connecticut and began an NIAAA funded alcohol research center – which carried out biological and behavioral studies of craving, medication development and heritability. He was among the 1st to show that psychopathology was a predictor of treatment outcome in alcoholism.

Dr. James Woods has been carrying out pioneering animal work on opioids, central stimulants and sedatives at the University of Michigan and is now trying to develop new pharmacotherapies for cocaine. In collaboration with Schuster he was 1st to show conditioned increase of morphine self-administration in monkeys.

Dr. Mark Schuckit is best known for his work on genetic factors in alcohol disorders. Most important was a 25-year follow-up study with an extraordinary 94% follow-up rate for 1600 subjects. His results showed that a low level of response to alcohol characterized children of alcoholics and other groups at high risk for alcoholism and can be a useful predictor of future heavy drinking and alcohol problems. In later work, recognizing that genes associated with alcoholism only explain half the risk, he found potentially important meditational roles for heavy drinking peers, positive expectations of the effects of alcohol and intoxication, suboptimal coping mechanisms, and comorbid psychiatric disorders.

Drs. Beny Primm and Roy Pickens both played key governmental roles in the late 1980's and early 1990's, in helping combat HIV. Because of new medications, this has now become in this country more of a chronic disease than the death sentence of the earlier years. Primm in 1969 set up the 1st minority - run M.M. program in the U.S. in New York (ARTC). In 1971 he joined Jaffe at SAODAP and went with him to Vietnam to set up the 1st in – country testing and treatment program. He became the 1st director of the Center for Substance Abuse Treatment (CSAT), now part of SAMHSA. He has been a major advocate for integrating HIV treatment into substance abuse centers. Pickens in addition to his HIV work carried out twin studies in relation to alcoholism.

Dr. Nora Volkow carried out her pioneering imaging work at Brookhaven National Laboratory from 1987 until 2003 when she became the Director of NIDA. Her research has been instrumental in changing the view of addiction from a behavioral choice to a brain disease and has shed light on the neurobiology underlying motivation and self-control, emphasizing especially the role of dopamine. Viewing addiction as a chronic and relapsing disorder of the brain, she has argued for it to be treated as a medical disorder rather than as criminal behavior. In normals, reinforcing effects of these drugs of abuse are associated with sharp increases in dopamine but in addicted individuals such drug-induced dopamine increases are markedly attenuated. Instead there is a heightened response to conditioned cues. Decreased D-2 receptors are also found in a number of addictive behaviors. Recently she was named U.S. News and World Reports "Innovator of the year" and has received a number of other awards.

VOLUME SIX: INTERVIEWEES AND INTERVIEWERS

Martin W. Adler interviewed by Larry Stein

Herbert Barry III interviewed by Thomas A. Ban

Jack Blaine interviewed by Leo E. Hollister

Kanellos D. Charalampous interviewed by Thomas A. Ban

Jerome H. Jaffe interviewed by Leo E Hollister

Donald R. Jasinski interviewed by Leo E. Hollister

Herbert D. Kleber interviewed by Andrea Tone

Gerald D. Klee interviewed by William T. Carpenter, Jr.

Conan Kornetsky interviewed by George F. Koob

Mary Jeanne Kreek interviewed by Lisa H. Gold

Roger E. Meyer interviewed by Thomas R. Kosten

Ernest P. Noble interviewed by Edythe D. London

Charles P. O'Brien interviewed by Leo E. Hollister

Roy Pickens interviewed by Leo E. Hollister

Beny J. Primm interviewed by Nancy Campbell

Joseph C. Schoolar interviewed by David Healy

Marc Schuckit interviewed by Andrea Tone

Charles R. Schuster interviewed by Thomas A. Ban

Nora D. Volkow interviewed by Charles P. O'Brien

Leonge E. Way interviewed by Lynn E. DeLisi

Matthew J. Wayner interviewed by Paul R. Sanberg

James H. Woods interviewed by David Healy

Chapter 7

Volume 7

SPECIAL AREAS

Desiderata

Barry Blackwell

The formal title of Volume 7 is “Special Areas”. But special in what way? As editor I chose the subtitle, “Desiderata”, defined by the Oxford English Dictionary as “something that is needed or wanted”. Our field of enquiry did not come into existence complete or without the support of allied disciplines and scientists who have distinguished themselves in its lesser known areas. The twenty-nine interviews in this volume fall into one or more of five categories. The “Orphan” areas (children, the elderly, women of childbearing age), Overlooked areas (such as aggression, late onset schizophrenia and hormonal disorders), Mechanisms of Action (such as neuropathology, genetics and animal models), Methods of Definition (outcome measures and nosology), and Novel Treatments (nerve and brain stimulation).

This Volume is dedicated to Lou Lasagna, ACNP President in 1980. Often considered “the father of clinical pharmacology” he established the first department of this new discipline at Johns Hopkins University in 1954 just as the first modern drugs became available to treat mental illness. In 1962 his expert testimony to Congress set the standards for controlled clinical trials, helped establish the first prescription drug laws in the world and set evidentiary standards for the FDA and pharmaceutical industry.

The contents of the interviews are summarized in two ways. The series editor, Tom Ban, provides a brief account of each interviewee’s scientific accomplishments supported by 343 key references while the volume editor, Barry Blackwell, summarizes the characteristics of the people and the circumstances that enable their contributions.

Six interviewees contributed to Child Psychiatry. Kaufman spent a lifetime defining the etiology, manifestations and treatment of phenylketonuria. Conners identified minimal brain dysfunction and devised rating scales to measure its characteristics and response to treatment. Wender studied the pharmacology of minimal brain dysfunction in children and adults. He also collaborated with Kety and Rosenthal in epidemiologic studies of schizophrenia in biological or adoptive families and introduced the concept of spectrum disorders. Rapoport studied the pharmacology of attention deficit and obsessive compulsive disorders in children. Rachel Klein explored the benefits of imipramine in separation anxiety disorder and pemoline or methylphenidate in conduct disorders. She also demonstrated that behavior therapy added no benefit to medical treatment of ADHD.

Five interviewees worked in Geriatrics. Blazer explored the epidemiology and genetics of melancholia. Reisberg developed rating scales to measure the effects of psychotropic drugs in the elderly and was among the first to study memantine in Alzheimer's disease. Chase defined the clinical, pathological and therapeutic aspects of Alzheimer's and Parkinson's disease. Jeste studied late onset schizophrenia, age as a risk factor in tardive dyskinesia and the frequency of psychotic symptoms in Alzheimer's disease. Alexopoulos explored the relationship between neuropathology and depression in the elderly as well as differences in placebo response with age.

Seven of the interviewees contributed to Descriptive Psychiatry. Clayton furthered the diagnostic concepts of bipolar and schizoaffective disorder and the separation of bereavement from depression. Later work was on the relationship of nortriptyline plasma levels with outcome in depression followed by collaboration with Angst on mortality rates in mood disorders. Endicott with Spitzer developed the Research Diagnostic Criteria (RDC) and the Schedule of Affective disorders (SADS) which contributed to the development of DSM III. Later on she contributed to the definition of premenstrual dysphoric disorder. Dunner conducted genetic studies on manic-depression that led to the recognition of Bipolar Disorder Type II and, working with Fieve, he developed a taxonomy of bipolar disorder that included "rapid cycling". Akiskal studied and helped develop a taxonomy of affective disorders including the relationship to personality and psychopathology leading to the concept of bipolar spectrum disorders. Halbreich with Endicott described the relationship of premenstrual dysphoria to depression and later explored the relationship between gonadal hormones and menstrual disorders including their

treatment with antidepressants and hormones. Halmi studied eating disorders and their variable response to psychotropic medications. Later she explored the biological similarities between anorexia nervosa and depression also collaborating in the discovery of a susceptibility gene for anorexia. Eichelman studied the pharmacology of aggression in animals and humans and later developed the Carolina Nosology of Destructive Behavior.

Three of the interviewees engaged in Pharmacokinetic Research. Cooper, in a lifetime of research at the Nathan Kline Institute, developed methodology to study plasma and tissue levels of numerous psychotropic drugs. In collaboration with clinicians he demonstrated the reliable relationship of 24-hour lithium levels to ultimate dose requirements in bipolar disorder. Glassman studied the effects of imipramine plasma levels on cardiovascular effects and psychotic depression. Later research was on smoking cessation including its relationship to major depression and treatment with clonidine. Dahl worked on the pharmacokinetics of chlorpromazine followed by use of plasma level monitoring of antipsychotic drugs. Later work was on modeling of neurotransmitter receptors and structure-activity relationships.

Two interviewees contributed to Novel Biophysical Treatments. George was first to employ transcranial magnetic stimulation (TMS) as well as vagal nerve stimulation. Lisanby has continued work on TMS in the treatment of depression.

Five interviewees have worked in the areas of Mechanisms of Action and Causation. Arango studied the relationship of serotonin and its receptor sites in suicide victims and major depression. Costa, during a prolific career, studied the neurochemistry of serotonin and its receptors; the mode of action of gabaminergic receptors with benzodiazepines and the role of reelin protein, mDNA and numerous physiological mechanisms in both schizophrenia and manic depressive disease. Kupfer extensively studied the phases of sleep in relation to characteristics of depression and the response to treatment in both insomnia and depression. McKinney early on studied the effects in monkeys of reserpine and chlorpromazine and later wrote a monograph on Animal Models of Mental Disorders. Shooter isolated and characterized nerve growth factor and later, with others, a neurotropic factor involved in myelination.

The background of the twenty-nine interviewees in Volume Seven varies widely but all are members of the ACNP who entered the field at different stages in the evolution of neuropsychopharmacology, covering fifty years of history.

Eight of them came from foreign countries when America was indeed the "land of opportunity" with NIH grants and fellowships available to support talented young researchers. The National Institutes played a valuable role in the careers of every scientist in this volume except one. Twelve held fellowships or leadership positions at the NIMH, a few for many years and the others had significant grant support. One striking demographic reflects a changing cultural ethos between the 22 pioneers in Volume One (Starting Up) and this volume; all of the interviews in Volume One were men but almost a third were women in Volume Seven (9 of 29). All of the earlier pioneers were MDs while in this volume seventeen are MDs, eight are PhDs, three are MD/PhDs and one is a laboratory scientist. This reflects the widening scope of a developing field and underscores the fact that scientific innovation is facilitated by interdisciplinary collaboration and translational dialogue.

Personal attributes confirm what is already known about the process of scientific discovery. The individuals were all young at the time of their peak creativity and exceptionally bright, many with scholarships, graduate honors and prestigious fellowships under outstanding mentors. They were strongly motivated as evidenced by early publications (often as students or residents), accelerated academic promotion and purpose driven lives. Many were exposed to research either on a voluntary basis or as a curriculum requirement, as undergraduates, medical students, residents or graduates. As a group they showed an early propensity for critical, creative and flexible thinking often derived from early philosophical, parental or mentoring experiences. All this contributed to a willingness to challenge the prevailing Zeitgeist in America that was strongly psychoanalytic. To do this also required self-assurance, an element of risk taking and curiosity. The importance of mentors and role models was ubiquitous. Sometimes these were parents but more often teachers and faculty members in places like George Washington University, Saint Elizabeth's Hospital in Washington DC or the NIMH, places where data based critical thinking was beginning to challenge psychoanalytic hegemony.

Research output, measured by scientific publications, books, book chapters and grants awarded ranged from productive to prolific. It was nurtured by a climate in which new findings

were frequent and, as one scientist remarked, almost everything they touched was statistically significant. This natural feedback was highly reinforcing and the result was often reflected in membership of advisory, research or editorial boards and national or international recognition awards.

But not everything was plain sailing. Concerns were expressed by several investigators about the shortcomings of DSM nosology and the FDA's rigidity in applying it to clinical trials. Criteria were sometimes derived from consensus between competing ideologies and on an archaic principle of symptoms that convey clinical homogeneity but might conceal biological diversity, (as with pain, fever or high blood pressure). This impasse occurred in pre-menstrual mood changes, some pediatric and geriatric conditions and in aggression. A second area of concern was the influence of the press, public opinion and the Church of Scientology on research and treatment of eating disorders, ADHD, ECT and aggression.

Financial issues are an increasing concern. Early on there was ample support from NIH which greatly exceeded that from Foundations or pharmaceutical companies. Federal grants are now more competitive and the cost of research has increased making it difficult to fund multicenter studies with large sample sizes. The fiduciary influence of the pharmaceutical companies raises concerns about a corrupting influence in education and research, perhaps diverting the best clinical minds away from psychopharmacology.

A repetitive theme among scientists in this volume is dedication to clinical work as the seedbed for research hypotheses. Another is to becoming mentors for the next generation of neuroscientists. Finally there is a strong consensus about the ACNP's positive influence on research productivity and interdisciplinary dialogue. If there is any wish it is that the organization might play a more prominent national role in addressing the areas of concern noted in this volume. One of the interviews provides an in depth analysis of the ubiquitous influence of the ACNP on the field and its members as well as a thoughtful dissection of its virtues and shortcomings.

VOLUME SEVEN: INTERVIEWEES AND INTERVIEWERS

Hagop S. Akiskal interviewed by Paula J. Clayton

George S. Alexopoulos interviewed by Andrea Tone

Victoria Arrango interviewed by Andrea Tone

Dan G. Blazer interviewed by Andrea Tone

Thomas N. Chase interviewed by ThomasA. Ban

Paula G. Clayton interviewed by Thomas A. Ban

C. Keith Conners interviewed by Burt Angrist

Thomas B. Cooper interviewed by Thomas A. Ban

Erminio Costa interviewed by Stephen Koslow

Svein G. Dahl interviewed by Andrea Tone

David L. Dunner interviewed by Thomas A. Ban

Burr S. Eichelman interviewed by Thomas A. Ban

Jean Endicott interviewed by Darrel A. Regier

Barbara Fish interviewed by Maria Meldrum and Elizabeth Bromley

Mark S. George interviewed by Robert Post

Alexander H. Glassman interviewed by Thomas A. Ban

Uriel M. Halbreich interviewed by Daniel P. van Kammen

Katherine A. Halmi Interviewed by Thomas A. Ban

Dilip V. Jeste interviewed by Thomas A. Ban

Seymour Kaufman interviewed by Thomas A. Ban

Rachel G. Klein interviewed by David Healy

David J. Kupfer interviewed by Alan F.. Schatzberg

Sarah Hollingsworth Lisanby interviewed by Andrea Tone

William T. McKinney interviewed by Thomas A. Ban

Judith L. Rapoport interviewed by David Healy

Barry Reisberg interviewed by Elizabeth Bromley

Eric M. Shooter Interviewed by Thomas A. Ban

Myrna M. Weissman Interviewed by Thomas A. Ban

Paul H. Wender interviewed by Thomas A. Ban

Chapter 8

Volume 8

DEVERSE TOPICS

Carl Salzman

It is a pleasure to introduce volume 8 of the Oral History of Neuropsychopharmacology. Ail of the interviewees are well known for their research, their teaching and for their leadership roles in administration of academic, industrial, or public health programs.

Several characteristics in this volume emerge with striking emphasis. Before becoming scientists, nearly all had diverse interests: musicians, English majors, non-psychiatric physicians, and the usual confused young people who were uncertain about their future paths. The few who were interested in science often came into the field through early laboratory experience, working in hospitals or health care facilities. Virtually all received their psychiatric training at the leading academic psychiatry residencies; a majority received part of their training at NIMH, and some remained at NIMH for part or all of their careers.

It is also interesting that of the 24 ACNP members who were interviewed for this volume, 7 (a little less than 1/3) had an initial interest or were studying psychoanalysis before they became interested in psychopharmacology. At least 3 continued to practice psychoanalysis as they began their scientific career, and two continued to be a practicing psychotherapist/analyst during their entire psychopharmacology career. On the other hand, several of the interviewees described their extreme displeasure and disillusion with psychoanalytic theory and treatment early in their career, amounting almost to repugnance!

Everyone interviewed stressed the importance of mentors early in their careers. Some of these mentors became close personal friends and there are many amusing anecdotes of interactions between mentor and junior colleague.

As a group, these 24 interviewees were fantastically successful in their careers. In

academia, most of them were full professors, many with endowed chairs, and some were chairs of leading departments of psychiatry. A few became Deans and one is President of a large hospital. Leadership roles also extended to industry and to large public health systems. Everyone served on editorial boards of leading journals (several created their own journals), and in leadership roles in professional organizations. Most, if not all, received awards for excellence (some received numerous awards) for outstanding contributions to science and education. In all, a very, very impressive group of individuals!

As might be expected, everyone interviewed lauded the role of ACNP in their careers. Specific mention was made of the structure of the annual meeting: the mixing of formal presentations, informal gatherings, and teaching programs. For virtually all, the annual meeting was the highlight of each year.

Overall, the interviews not only provided an historical overview of the development of psychopharmacology through the eyes of some of its most illustrious leaders, but it also gave a wonderful perspective on the life course of some outstanding physicians, psychiatrists, psychologists, clinicians, educators, and, most of all, psychopharmacologists and neuroscientists. Like science itself, life does not always proceed on a direct and predictable path, and these interviewees often demonstrated resilience and flexibility in their career paths.

Among the many contributions of this group of ACNP members, significant advances in neuropsychopharmacolgy were made. For example, neuropsychopharmacological studies in stress (Maickel); demonstration of the human growth hormone (HGH) response to clonidine, is significantly different (reduced) in patients with endogenous depression from normal subjects, and from patients with schizophrenia and neurotic depression. (Ackenheil); research promoting the use of cholinesterase inhibitors for Alzheimer's disease (Davis); spearheaded the implementation of the double-blind, placebo-controlled randomized clinical trial (RCT) in the clinical development of psychotropic drugs and shaped the FDA regulations relevant to the approval of psychotropic drugs for clinical use (Leber); developed and launched olanzapine for the treatment of schizophrenia (Beasley, Tollefson); clinical research in redefining the characteristics of affective illness (Judd, Gazner, Frank); teaching of psychopharmacology including the development of a model curriculum to teach psychopharmacology (Stahl; Shader, Salzman, Glick); the relationship between changes in biological measures and treatment efficacy

in psychiatric disorders (Csekova); identification of potential susceptibility genes that increase the risk of developing schizophrenia (Kleinman); hypersecretion of corticotrophin releasing factor in depression (Nemeroff); studies on the role of the glutaminergic system in mental disorders (Henn, Coyle); changes in some .prostaglandins in the CSF of schizophrenics (Mathe); opening the path for extending the therapeutic indications of selective 5-HT reuptake inhibitors from depression to bulimia (Ebert); metabolic evidence of the induction of hepatic tryptophan pyrolase activity and marked reduction of urinary serotonin metabolites in depression (Mandell); psychological stress can change the structure and function of the brain (Charney); setting up data bases that would allows access to all information generated in neuroscience for analyses (Koslow).

VOLUME EIGHT: INTERVIEWEES AND INTERVIEWERS

Manfred Ackenheil interviewed by Andrea Tone

Charles M. Beasley, Jr. interviewed by William Z. Potter

Eva Ceskova interviewed by Andrea Tone

Dennis S. Charney interviewed by Andrea Tone

Joseph T. Coyle interviewed by Benjamin S. Bunney

Kenneth L. Davis interviewed by Stanley J. Watson

Micheal H. Ebert interviewed by Benjamin S. Bunney

Ellen Frank interviewed by William E. Bunney, Jr.

Peter Gaszner interviewed by Andrea Tone

Ira D. Glick interviewed by Donald F. Klein

Fritz A. Henn interviewed by Andrea Tone

George R. Heninger interviewed by Thomas A. Ban

Lewis L. Judd interviewed by Andrea Tone

Joel E. Kleinman interviewed by Elizabeth Bromley

Stephen H. Koslow interviewed by Thomas A. Ban

Paul Leber interviewed by Thomas A. Ban

Roger Maickel interviewed by Leo E. Hollister

Arnold J. Mandell interviewed by David Healy

Aleksander A. Mathé interviewed by Leo E. Hollister

Charles B. Nemeroff interviewed by Thomas A. Ban

Carl Salzman interviewed by Roger E. Meyer

Richard I. Shader interviewed by Carl Salzman

Stephen M. Stahl interviewed by Andrea Tone

Gary D. Tollefson interviewed by Joel Braslow

Chapter 9

Volume 9

UPDATE

Barry Blackwell

Volume 9, “Update” differs from the first eight volumes. It includes second interviews of 20 influential pioneers conducted between one and fifteen years after the original interview (from 1997 to 2008). Where appropriate the series editor, Tom Ban, documents the interviewees continuing contributions and places them in the larger scientific context supported by over 200 references. The volume omits detailed biographical material that is found in Volumes 1 thru 8 in each editor’s Dramatis Personae.

The introduction by the volume editor, Barry Blackwell, fulfills a major purpose for this update – to focus less on each person’s considerable accomplishments and to provide an overview of the field by its leading protagonists. Two were part of the six member ACNP organizing committee (Ayd and Cole); eight were founding members in 1961 (Ayd, Cole, Costa, Fink, Gottschalk, Hollister, Kornetsky and Sarwer-Foner); four became Presidents over a quarter century (Cole, ’66, Hollister ’74, Don Klein ’81, and Simpson ’91) and five received the Paul Hoch Distinguished Service Award (Ayd, Ban, Cole, Hollister and Don Klein).

Volume 9 is dedicated to Nathan S. Kline, a founding member and sixth President (1967). Nobody better personifies the pioneering spirit that initiated the field of neuropsychopharmacolgy. “Nate” was intensely creative, energetic, curious, challenging and entrepreneurial. A two time winner of the Laskar Award he died at the early age of 67 in 1982 before the history project began. Those interviewed in this volume reflect the scientific and cultural Zeitgeist of the mid 1950’s. They include only one woman, Rachel Klein, who became a member of the ACNP in 1973. Clinicians far outnumber basic scientists; seventeen, were physicians although two were devoted to neuropharmacology (Berger and Pletscher) and three

were psychologists (Katz, Kornetsky and Rachel Klein). Today the ACNP is split almost equally between MDs, PhDs and those with both credentials.

While everyone is distinguished in their field different career patterns are apparent. Two clinicians stressed the diversity of their contributions. Hollister says, “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 wanted to go. In the same vein Janowsky states, “I’ve done a number of different things at different times and I haven’t done any one in great depth. I liked the idea of being an innovator, getting in and getting out; of course that has a strong disadvantage because the ethos of science is linear and in depth”. Contrast this with Kaufman’s lifelong career devoted to the causes and treatment of phenylketonuria. Clearly there are also hybrid forms that include both types of accomplishment. In his interview with Don Klein, John Davis considers the persistence that led to the definition, treatment and potential biochemical etiology of panic disorder to be of “Nobel Prize caliber”. But Don made many other contributions to the field in a variety of different areas.

These interviews make the reader aware of the climate of innovation involved in a scientific paradigm shift. Don Klein notes that when he went to medical school in1949 “I believe every Chairman of Psychiatry in the United States was a psychoanalyst”. An interest in drugs and clinical trials was attributed by his analyst to sadism. But not every budding psychopharmacologist had to be a Don Quixote; some psychoanalysts adapted creatively to the new discipline. Two were founding members of the ACNP in 1961 and are represented in this volume. Sarwer-Foner, a lifelong friend of Delay and Deniker who pioneered chlorpromazine, practiced a unique form of clinical approach that combined analytic and pharmacological insights in a manner prescient of Don Klein’s concept of “pharmacological dissection”. The career of Lou Gottschalk shows a similar pattern of innovative adaptation. He combined graduate work in neurophysiology with psychoanalytic training that led to lifelong research in verbal content analysis where he established the reliability and validity of the method before computerizing it. “I like to listen to language. How do psychiatrists learn anything about anybody?”

Collectively these interviews reflect a rewarding environment that reinforced innovation and curiosity. Frank Ayd notes, “It was the best time to do research”. A time when attention

focused sharply on each patient's response to promising new treatments. The methods to study this new arena were also exciting and novel. Hollister comments, " Back when John Overall and I were working and nobody knew what the best ways were to give drugs, what were the best ways to use rating scales or what were the best statistical procedures it was something you could contribute that was original and scientific". Rachel Klein concurs that freedom from pre-existing assumptions was an asset. "The ethos of the research department was that we knew very little, I was very impressed with this ability to acknowledge ignorance". Pletscher comments on both the scientific and commercial appeal of a scientific vacuum. When he left the NIH to work in industry he "told top management that the primary area of research must be psychotropic drugs". Berger was more succinct, "They (management) wanted me to find drugs with a big market". And so he did, with meprobamate (Miltown). It was not only the drugs and research strategies that were new, so were the patients and the positive feedback they provided clinicians. Simpson comments, "Patients had never used drugs before and you really did see patients who would tell us they felt better than in their whole life. They improved dramatically". Positive feedback was scientific as well as psychosocial. Study populations were naïve, uncontaminated and not saturated with treatment resistant individuals. New basic science techniques also yielded novel findings. Van Praag notes, "There were new discoveries almost every month, so it was a very exciting time".

The interviews convey the exciting climate and hopes for the future but what do they say about the outcomes fifty years later? Even after subtracting for nostalgia it would be Pollyannaish to deny some discontent, disappointment and frustration. Things were not as simple or predictable as the pioneers hoped or expected.

Despite a plethora of rating scales, diagnostic checklists and statistical techniques clinical trials were largely unable to distinguish between drugs even when they had different neurochemical actions. Listen to Hollister, "To find the right drug for the right patient has been a frustrating experience" and Itil laments " We don't know the cause of any psychiatric illness and therefore we don't have a real treatment for any of them". Janowsky identifies another flaw, "We've thrown out a lot of things that are important in research by worshipping the god of obsessionality … the person who wants to look in a decidedly different direction is often considered 'out to lunch'". Katz believes these barren outcomes are because trial methodology

supports a commercial rush to establish statistical efficacy before the therapeutic process is fully understood particularly in the early days of treatment, “Why have we not completed the story of how these drugs work therapeutically in patients”. Don Klein notes how errors in logic compound faulty observation, “They think if two conditions both respond to the same drug it must be the same condition”. Complexity also trumps simplicity at the biochemical level. Costa states this eloquently, “One receptor does many different things than just the one you’re interested in … drugs that are successful are those that target three or four receptors … no transmitter regulates a particular function”. Those addicted to Occam’s razor or the lure of simple unifying models learned to be disappointed. As Itil puts it, “Every ten years we have another hypothesis for depression. In my lifetime we have had four different hypotheses, obviously none of them is true”.

The paradigm shift from psychoanalytic to a psychopharmacologic model demanded a nosology revolution to better know and recognize what we were treating; from opinions based on anecdotal case studies to trial designs that protected from bias. So rating scales, the DSM system, double-blind controlled studies, complex statistical analyses and FDA regulations were all desirable developments that brought their own downside. Also, on the positive end, hundreds of thousands of people who suffered in mental asylums and prisons now had access to medications that helped even if they didn’t heal. But this too came at the cost of an expanded and pervasive role for the pharmaceutical industry bringing conflicts between commerce and science. These benefits and costs are reflected in the interviews.

Rating scales and statistical techniques were sometimes ambivalently viewed. Ban states, “For me changes in the psychopathological symptom profile of individual patients were far more informative than changes in rating scales”. And also, “We had numerous statistically significant findings but none of them was of clinical significance”. Statistical fads that replaced old fashioned ways of evaluating data were not always an advance in Don Klein’s opinion, “Extremely detailed literature review has been replaced by meta-analysis, which is much worse in every way”. Long the gold standard, double-blind controlled studies were seen to be flawed due to short durations, highly selected patient samples and unnatural compliance which highlighted the distinction between efficacy and effectiveness revealed in the CATIE study. Fink tells us, “I have stopped using any drug produced after 1980. None has been tested independently

and with time their inefficacy and risks are better understood". Flaws in the DSM system became increasingly apparent; Hollister notes, "Anytime things get standardized, that's an excuse to stop thinking". Rachel Klein elaborates, "It has not fulfilled its promise. We have adopted a checklist approach to diagnosis and the sense of what has gone wrong has been lost. The DSM was never intended to be a formula or rule. It was to be a guide for clinical purposes". Don Klein has an added concern; "DSM has deflected clinicians away from taking detailed developmental histories … many, including scientists, made the unwarranted assumption that these clearly heterogeneous syndromes had a homogeneous etiology". He believes that the FDA, industry and the NIMH have all failed to support efforts to "detect specific pathophysiologies". Van Praag makes the succinct scientific objection to the DSM, "If we use the DSM diagnostic entities we will never progress in biological psychiatry". Katz summarizes these concerns, "The DSM system has become an impediment … if we don't transfer reliance on that diagnostic system to changes in behavior, mood and cognitive function we will never learn the nature of the elemental interaction between chemistry and behavior that determines what is going on in the therapeutic process".

Another broad area of concern is the shifting role of individuals, the industry and NIMH in the design, support, conduct and analysis of clinical studies. The first pioneer clinical studies were by individuals in practice (like Ayd and Sarwer-Foner) then by work in State hospitals and the VA (Kline, Simpson, Hollister), next by the NIMH Early Clinical Drug Evaluation Units (ECDEU) and eventually in academic medical centers. As the complexity and cost of research escalated and the number of breakthrough drugs dwindled each of these agencies was forced out of business. The interviews document this process leading to the closure of the ECDEU, a switch from clinical to basic science at the NIMH and increasing dominance by industry. Itil comments, "When the ECDEU program was dissolved investigators became dependent completely on drug companies". Janowsky is outspoken, "The value system has become money and technique bound, as opposed to discovery bound. I think the value system is sick". Hollister details this concern in his customary salty language, "The drug companies have big groups of people designing protocols, rating scales and report forms, analyzing statistics. It reduces the investigator to a mere peanut gallery and most of the studies are done by flunkies they hire so there's no scientific input at all. Well, that's a hell of a way to do things".

The interviews also document a widespread concern about the corrupting influence of commerce by dubious direct advertising to the public and primary care doctors (Simpson), as well as by a ubiquitous involvement in every source of information to physicians including medical schools, conferences, seminars, doctor's offices, professional and advocacy organizations. Fink, a self-described Don Quixote, claims, "The APA has now been taken over by industry. The ACNP has made an attempt, I understand, to deal with the issue but leaders of the society are intimately tied to industry". Janowsky concurs, "We have become perverted as a system at the natural level in our own minds and in our universities". Addressing the basic problem of how industry attempts to inflate the efficacy of newer more expensive drugs Hollister opines, "…if you're buying expensive drugs and have to give up the rest of treatment, that's a bad bargain".

A final area of concern and regret is the feeling by some that promising ideas have been prematurely abandoned due to changes in funding priorities affecting a field in a hurry and a preoccupation with productivity over discovery. Examples include conditioned response variables (Ban), the pharmaco-EEG (Fink) and verbal content analysis (Gottschalk). Other regrets include loss of intimacy, collegiality and clinical expertise as the field has increased in size and complexity with a perhaps disproportionate turn toward basic neuroscience. Simpson notes, "It's easy to focus on these new methods and under estimate the value of clinical contributions". While that balance has shifted it is well to remember that animal neurochemistry and physiology needs to be correlated with human thought, feelings and behaviors. The interviews express concerns that our capacity to accomplish this translation has been blunted and dulled by decline in the quality of clinical drug evaluation.

Faced with the disappointments of the past fifty years hopes for the future are tinged with the skepticism experience has imposed. It is as if industry is unwittingly killing the goose that lays its golden eggs.

Despite this gloomy conclusion those who have contributed their careers to psychopharmacology have few, if any, regrets. Janowsky sums it up by saying, "It never felt like work or that I was doing it for money. Somebody was paying me to do the things I would probably have done as a hobby". Levine echoes that sentiment, "There are a lot of definitions of

utopia and mine is when someone will pay you for the work you love to do; that's how I feel about psychopharmacology".

Whatever the accomplishments of the next fifty years may be, these sentiments are a benediction to be wished for on behalf of future generations of psychopharmacologists.

VOLUME NINE: INTERVIEWEES AND INTERVIEWERS

Frank J. Ayd, Jr. interviewed by David Healy

Thomas A. Ban interviewed by William E. Bunney, Jr.

Frank M. Berger interviewed by Thomas A. Ban

Jonathan O. Cole Interviewed by Thomas A. Ban

Max Fink interviewed by David Healy

Louis A. Gottschalk interviewed by Thomas A. Ban

Leo E. Hollister interviewed by Thomas A. Ban

Turan M. Itil interviewed by Andrea Tone

David S. Janowsky interviewed by Burt Angrist

Martin M. Katz interviewed by Stephen M. Koslow

Donald F. Klein interviewed by John M. Davis

Rachel G. Klein interviewed by James F. Leckmann

Conan Kornetsky interviewed by Thomas A. Ban

Jerome Levine interviewed by William T. Carpenter, Jr.

Herbert Y. Meltzer interviewed by Carol A. Tamminga

Alfred Pletscher interviewed by Andrea Tone

Gerald J. Sawrer-Foner interviewed by Joel Braslow

George M. Simpson interviewed by Thomas A. Ban

Herman M. van Praag interviewed by Robert H. Belmaker

Chapter 10

Volume 10

HISTORY OF THE AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

Martin M. Katz

My mission is to cover some of the highlights of the volume.

I begin with a quotation from Arvid Carlsson. He's reflecting on a scientific issue central to the College's mission for several decades, about the direction of research in the field. *"Drugs don't care about the boundaries between one diagnosis and another"*. I believe that this is a simple but profound statement, highly relevant to the manner in which researchers (basic and clinical) have gone about investigating the mechanisms of drug action and determining the nature of their clinical actions. On (the issue of mechanisms, we have over the years, witnessed increasing advances in the technology aimed at uncovering the neurochemical bases for the success of the drugs in resolving the dysfunctions underlying the mental disorders. During this period (marked by literally thousands of studies) we have at the same time, stumbled somewhat in attempting to elaborate the drugs' clinical actions. For example, for more than two decades, it has been entrenched in textbooks, that the clinical actions of antidepressants (1) lag several weeks in their timing, behind their almost immediate neurochemical actions; (2) the drugs are specific in their actions to the depressive disorder; and (3) the different classes, the SSRIs and the tricyclics, initially impact the same symptoms. These ideas on clinical actions have all turned out, on the basis of more recent targeted studies, to be incorrect. They are assumptions that underlied much basic and clinical investigation during this period and led to an unnecessary delay in elaborating the actual basis of the drugs' capacity to resolve these disorders. Consequently, these false notions have delayed the advance of the science and the development of more rapidly acting, more effective antidepressants. The basis for this misdirection, shown in Table 1, are the assumptions listed in column 1.

Table 1

Assumptions that Currently Guide Most Clinical Research on Antidepressants vs. Evidence-Based Findings

Assumptions	Findings from NIMH CDS[a] & Texas Study
1. Antidepressants (ADs) are specific for treatment of depressive disorders.	1. ADs are specific for reducing anxiety, depressed mood, hostility and motor activity.
2. Clinical actions of ADs lag several weeks behind almost immediate effects on central neurotransmitters.	2. ADs initiate improvement in anxiety and hostility within the first week of treatment; full response in treatment-responders in 4 to 8 weeks.
3. TCA[b] AD's induced marked reductions in CSF[c] concentrations of neurotransmitter metabolites are associated with reduction in severity of depressive disorder.	3. TCA induced reduction in CSF concentration of serotonin metabolite was associated with reduction of anxiety; norepinephrine metabolite, with reduction of motor retardation.
4. Depression is a unitary disorder with depressed mood and motor retardation reflecting its core dimension.	4. Depression is multifaceted in composition, comprised mainly of the interaction of 3 dimensions, anxiety-agitation, depressed mood-retardation and hostility-interpersonal sensitivity.
5. The different types of ADs effect the same early changes in the disorder prior to clinical response.	5. The SSRI and NRI ADs, altho equally effective, induce different initial patterns of behavioral improvement.

a: NIMH Collaborative Study of Psychobiology of Depression[1]
b: Tricyclic Antidepressants cerebrospinal fluid[2]

These assumptions can be traced to the tendency to act as if the depressive disorder is unidimensional and, contrary to the Carlsson statement, that the drugs are “diagnosis-specific” in their actions. The assumptions conflict with the evidence (shown in column 2) that “depression” is multifaceted, comprised of several equipotent components or dimensions. The clinical trials model has failed to follow the path established in basic studies, i.e., the “profile of actions” approach, in elaborating the nature and timing of behavioral and mood changes induced by the new drugs. The substitution in trials, of diagnosis for delineation of the major behavioral components of the disorder (in clinical drug studies), has significantly impeded the advance of knowledge on basic neurobehavioral mechanisms and development of new drugs.

To turn now directly to the “history of the College”, it is important to observe, that after 50 years, the members generally, report being quite happy with the way the College has developed. Their statements identify the College, with its cross-disciplinary annual program and its unique social atmosphere, as their most favored scientific association. They continue to see the College as their best opportunity to meet the most prominent members in their field, the annual program, as the most fertile for generating new ideas, and the most profitable from the standpoint of advancing their careers.

Among the interviews in the Volume is the classic one that Fridolin Sulzer, as the Interviewer, masterly coaxes from founder, Joel Elkes . Elkes eloquently defines the conceptual foundation of the College and specifically, the “mission” of this unique multidisciplinary organization. He recognized, as did other Founders, that in attempting to merge the sciences, we had to overcome the diverse languages, training backgrounds, and the cultures that the different scientists and clinicians bring to their interaction.

They would have to develop a new language, one that could rapidly serve as the vehicle of communication for advancing the new science.

To accomplish that, he proposed (as one important step), the establishment of the “Study Group”. It was intended to target specific, tactical problems requiring interdisciplinary action, And later as we have witnessed over the years, the creation of “generational” volumes to cover the multiform, distinctive problems confronting the new science, leading eventually, to a new Journal in 1987 to keep pace with its rapid growth.

For the most part, the membership and the College Presidents report in Volume 10, being very pleased with the progress of the science and with the College's evolving and expanding role in leading the field into the future.

Nevertheless, there are some ripples of discontent. The most focal unrest is that with the "mission" of the College and how it has changed over the years and how its membership and its annual program have reflected these changes.

The Volume devotes two chapters to this central issue, the evolving mission as perceived by the basic and trans-disciplinary scientists, on one hand, and then, from the viewpoints of clinicians and clinical scientists, on the other. The Basic Scientists are relatively content here. Their proportion of the membership is now much larger (than in the beginning), and their view of the program is that it is in accord with current trends and advances in the relevant sciences. Contentment is not true for the Clinical Scientists. They see the clinical role, generally, and their impact on the new science, as being neglected; clinical science and practice, as currently, less central to the "mission" of the College. And their role, as reflected in the annual program, and their work, as steadily decreasing in importance. Because these issues are raised by so many members and because the clinical issue, the development of new treatments for the disorders, is so central to the mission, two chapters are devoted to represent the expressed views of John Davis, Frederick Goodwin and others of our leading clinical investigators.

Finally, I wish to make you aware of the inspiring interviews in the Volume with key Founders of the College. The Founders were:

1. Frank Ayd: The practitioner, who modestly characterized his early role as "sort of a John the Baptist, wandering in the wilderness and preaching the gospel of the psychopharmaceuticals and their potential value for people" to his psychiatrist brothers.

2. Jonathon Cole: The creative scientist administrator, leader for the NIH support role in the new field, and developer of the first cross-national, controlled clinical trial of the phenothiazines in the treatment of acute schizophrenia.

3. Joel Elkes: The innovator and academic who provided the theoretical foundation for the new College.

4. Thomas Detre: The Chairman, who led the way in radically changing Departments of Psychiatry and the education of young psychiatrists, and

5. The International Corresponding Members who provide a perspective on the College's impact on worldwide development of the new science, its influence on the establishment of like Colleges in Europe and Asia.

Quotations from these figures tell an interesting story about the early development of the College. (Table 2.)

Table 2

Founders' Quotations

"I was sort of a St. John the Baptist in the wilderness preaching the gospel of the psychopharmaceuticals and their potential value for people." - Frank J. Ayd Jr

"….if you're working with a drug in 100 patients and few of them hadn't said, 'Wow, do I feel better' then you probably haven't missed anything and it probably isn't going to turn out better than the placebo." - Jonathan O. Cole

"I felt time has come to establish a department of psychiatry which would first and foremost concentrate on translational and strictly clinical research to improve the management of the patients." – Thomas Detre

"…I had experimented with the term 'experimental. Psychiatry' in my head for some six months; a department which brings experiments to psychiatry, and I called the department, Department of Experimental Psychiatry." - Joel Elkes

I come full circle in my presentation of the Volume, pointing first to partially solved, important issues in the science. Finally, to expressing the concerns of clinical members that the College, in the content of its annual program and in the shrinking proportion of its clinical membership, may be somewhat off direction for the future. On that note of caution, I turn it back to our current membership to chart that future path for our still young and growing science.

References

1. Katz MM, Maas JW (1994) Psychopharmacology and the etiology of psychopathological states: Are we looking in the right way? Neuropsycopharmacology 10, 139-144

2. Katz MM, Maas JW, Frazer A, Koslow S, Bowden CL, Berman N, Swann A, Stokes P. (1994) Drug-induced action on brain neurotransmitter systems and changes in behavior and emotions of depressed patients. Neuropsychopharmacology 11, 89-100

VOLUME TEN: TABLE OF CONTENTS

CONCLUDING REMARKS

Thomas A. Ban

Thank you Marty and thank you panel members for presenting the highlights of one or more volumes in our series, as you see it. Now, it is my turn, and let me conclude this session by presenting the "highlights" of the entire series, as I see it.

The project that was to become the oral history series was initiated in 1993 by the late Oakley Ray. His objective was to "preserve the legacy" of the pioneer generation by videotaping peer-interviews with the pioneers. (See, Volumes 1 & 10).

In 2007 with ACNP's 50th anniversary in sight, the objective was extended on my initiative to turning the interviews into a ten volumes series in which each volume the story is told from a different vantage point and in a different perspective, and the volumes are drawn together by my prefaces, in which interviewees' salient research contributions are identified (micro-history) with information given for placing these contributions into the stream of history (macro-history). (See, Volumes 1 & 2).

The story covered in the series begins in the mid 1950s with detection of monoamine neurotransmitters in the brain and the introduction of the first set of therapeutically effective psychotropic drugs and the spectrophotofluorimeter. The capability to measure the changes induced by these drugs on monoamine concentrations in the brain led to the extension of behavioral pharmacology to neuropharmacology and the birth of neuropsychopharmacology, a new discipline, for studying the relationship between mental and neuronal events. (See, Volumes 3 & 5).

Early research in neuropsychopharmaclogy raised hopes that studying the mode of action of therapeutically effective drugs would provide information on the biochemistry of the disease treated. It was also envisaged that this information would guide research to develop rational pharmacological treatments. But this did not happen. Research centered on the monoamines, norepinephrine, serotonin and dopamine, drove psychotropic drug development in circles. To-

date we have no single clinically more selective or effective drug available for the treatment of psychiatric disorders than the ones introduced in the 1950s. (See, Volumes 3 & 4).

While psychotropic drug development was side tracked, with the recognition that the primary targets of psychotropic drugs in the brain were encoded by genes that were identified, a molecular genetic era was replacing the neurotransmitter era in neuropsychopharmacology in the 1990s. Similar to the early years of the neurotransmitter era when the perspective for the detection of the biochemical underpinning of psychiatric disease stimulated biochemical research in mental illness, the perspective in the new era for the detection of the genetic underpinning of psychiatric disease simulated genetic research in mental illness. But again, expectations were not fulfilled. Similar to the findings in biochemical studies, in the 1960s, 70s and '80s, findings in genetic studies in the 1990s and in the first decade of the 21st century, were inconsistent. (See, Volumes 3, 5 & 7).

What happened?

Introduction of psychotropic drugs focused attention on the pharmacologic heterogeneity within psychiatric diagnoses. To provide pharmacologically homogeneous treatment responsive populations for neuropsychopharmacological research, there was a need for a pharmacological re-evaluation of psychiatric diagnostic concepts. But, this did not happen. Instead, the randomized clinical trial (RCT) with consensus-based diagnoses and sensitive rating scales was adopted for the demonstration of therapeutic efficacy in pharmacologically heterogeneous populations. (See, Volume 4).

To ascertain that no molecule with psychotropic potential is overlooked, by the mid-1980s sample sizes in clinical drug studies were determined by power statistics; and to recruit the necessary number of patients in a reasonable period of time for these studies, single center drug trials were replaced by multi-center clinical investigations. As the same evidence based information, generated by RCTs is used in both, industrial marketing and academic education, these two complementary activities with opposite objectives, have become by confounded. (See, Volumes 4 & 8).

The replacement of psychopathology by psychiatric rating scale scores, and psychiatric nosology by consensus-based diagnostic algorithms, has profoundly affected psychiatry. It led to

an enlargement of the psychiatric population within some of the diagnostic groups, e.g., depression; extension of the scope of psychiatry from pathologies in mental processing to behavioral anomalies with compromised social functioning; and a new generation of psychiatrists familiar with brain imaging and molecular genetics but without any knowledge about the two disciplines that provided a foundation for psychiatry during the first fifty year of the 20th century. Gone with the two disciplines also is the memory that without the psychopathology based diagnostic concept of vital depression, the therapeutic effect of imipramine in depression might have been missed. (See, Volumes 7 & 9).

The pharmacological heterogeneity within psychiatric diagnoses has had a major impact on the development of neuropsychopharmacology. It prevented the generation of valid information on the biochemistry and (molecular) genetics of psychiatric diseases; blocked the development of rational pharmacological treatments; and interfered with the optimal use of psychotropic drugs. Fifty years of biological research in mental illness has not provided any cues for identifying treatment responsive sub-populations within psychiatric diagnoses. (See, Volume 5, 6 & 7).

As early as in the late 1950s, Fritz Freyhan, one of the founders of ACNP, focused attention on the need for a pharmacological re-evaluation of psychiatric diagnoses. Yet, it was only around the turn of the 21st century that "nosologic homotyping" with pharmacological validation, a clinical methodology for such a re-evaluation was proposed. The origin of neuropsychopharmacology was in Moreau de Tours' observation in the mid-19th century that patients with different mental pathology respond differently to the same drug. If this would be the case, pharmacologically validated "nosologic homotypes" should provide the necessary homogeneous populations in terms of psychopathology and psychiatric nosology for neuropsychopharmacologic research. (See, Volume 9).

It will remain for social historians to disentangle the reasons for the delay in addressing the need of a re-evaluation of psychiatric diagnoses. But be it as it may, the expectation of ACNPs founders that providing a forum for interaction between neuropharmacologists and psychopharmacologists would help narrow the gap between basic and clinical brain research was not fulfilled. With the rapid advances in neuropharmacology --moving from the study of the effect of psychotropic drugs on pre-synaptic uptake mechanisms, to post-synaptic membrane

receptors, second messenger mediated events, and early gene expressions-- psychopharmacology was left behind, and by the end of the 20th century the annual meetings of ACNP became dominated by basic research with no, or at best, questionable clinical relevance. (See, Volume 10). Even the "core purpose" of ACNP has changed during the years. It is no longer focused on the facilitation of neuropsychopharmacology research but "to contribute to alleviating human suffering by advancing the dissemination of knowledge related to the biology of the brain as well as the biology, prevention and treatment of brain disorders." An Oral History focuses attention on this development.

It also focuses attention on the need to develop a clinical methodology of neuropsychopharmacology for identifying treatment responsive populations to harmonize activities between basic and clinical research. By reviewing and reflecting on the history of the different areas of research under the umbrella of neuropsychopharmacology, we hope the series will provide an educational document that would help the field to achieve new success in the next fifty years.

In closing I would like to add that this series was created by an editors' team with the participation of almost 300 members of the College as interviewees and interviewers, with the dedicated help of Laura Bersacola Hill, ACNP's Project Coordinator and with the support of ACNP's Executive Director, Ronnie Wilkins. To all of them I would like to express my heartfelt thanks.

Thanks are due also to the 2011 executive and council of the College, for their approval for getting this series in print as an ACNP publication.

APPENDIX

Program for the ACNP symposium:

An Oral History of Neuropsychopharmacology:

Presented as a Plenary Session Panel at the 2011 annual meeting.

Waikoloa, Hawaii

December 7, 2013

Chair: Samuel Gershon Co-Chair: Martin M Katz

7:30 PM: volume 1: Starting Up (editor. Edward Shorter)
volume 2: Neurophysiology (editor: Max Fink)
Presenter: Edward Shorter

7:40 PM volume 3: Neuropharmacology
(The Neurotransmitter Era)
Presenter: Fridolin Sulser (editor)

7:50 PM volume 4: Psychopharmacology (editor. Jerome Levine)
Presenter: Donald Klein

8:00 PM volume 5: Neuropsychopharmacology (editor: Samuel Gershon)
Presenter: David Janowsky

8:10 PM volume 6: Addiction
Presenter: Herbert D. Kleber (editor)

8:20 PM volume 7: Special Areas (editor: Barry Blackwell)

volume 8: Diverse Topics (editor:.Carl Salzman)

volume 9: Update (editor: Barry Blackwell)

Presenter: Carl Salzman

8:30 PM volume 10: History of the American College of Neuropsychopharmacology

Presenters: Martin M. Katz (editor), John Davis

8:45 PM Discussant: Thomas A. Ban (series editor):