

**CELEBRATION OF THE 100 YEARS BIRTHDAY OF  
JOEL ELKES**

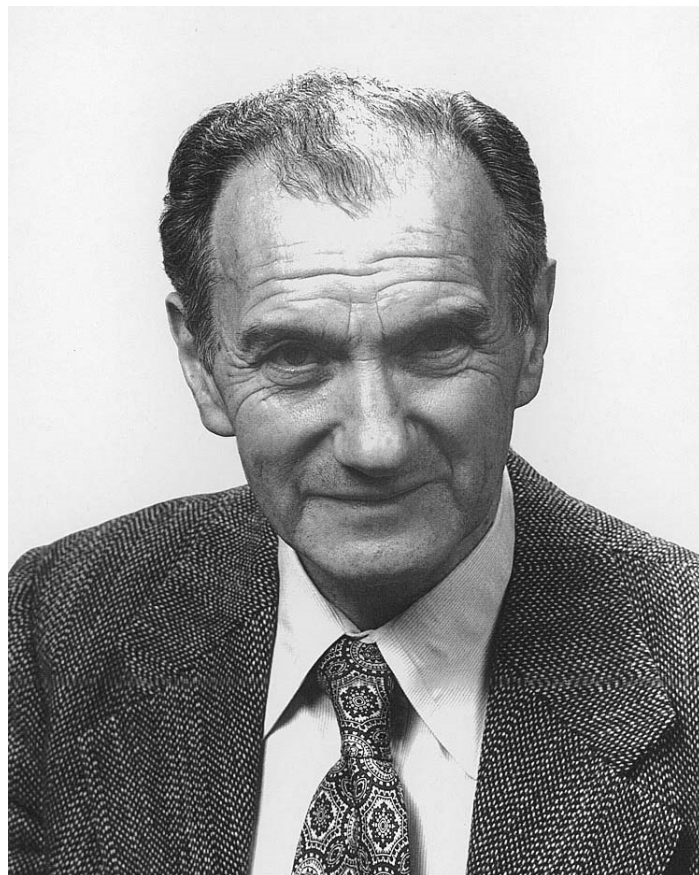
Edited

By

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International Network for the History of Neuropsychopharmacology

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**JOEL ELKES**

# **HAPPY 100 YEARS BIRTHDAY JOEL**

**American College of Neuropsychopharmacology (ACNP)**

**Collegium Internationale Neuro-Psychopharmacologicum (CINP)**

**International Network for the History of Neuropsychopharmacology (INHN)**

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## 1 INTRODUCTION

This E-book was prepared by the International Network for the History of Neuropsychopharmacology in honor of Dr. Joel Elkes CINP's Pioneer and ACNP's Founding President.

The material presented in this volume was adopted from the following ACNP and CINP publications with permission of the respective organization:

1. ACNP Bulletin 1962.
2. *The History of Psychopharmacology and the CINP, As Told in Autobiography*, Volume 1. *The Rise of Psychopharmacology and the Story of the CINP* (edited by Thomas A. Ban, David Healy and Edward Shorter). First edition: Animula 1998; Second edition: CINP 2010.
3. *CINP International Photo Archives in Neuropsychopharmacology 2000* (edited by Thomas A. Ban, Helmut Beckmann and Oakley Ray). Animula 2000.
4. *Selected Writings of Joel Elkes* (edited by Thomas A. Ban), First edition: Animula 2001; Second edition: CINP 2010.
5. *An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews* (edited by Thomas A. Ban), Volume 1, *Starting Up* (edited by Edward Shorter) and Volume 10, *History of the ACNP* (edited by Martin M. Katz). ACNP 2011.

*Celebration of the 100 Years Birthday of Joel Elkes* was posted on INHN's website (in "previews") on November 7, 2013.

## 2 BIOGRAPHIC INFORMATION

Detailed biographic information on Joel Elkes is presented in Thomas A. Ban's Foreword to *Selected Writings of Joel Elkes*. (Animula 2002; CINP 2010).

There is also some biographic information on Joel Elkes in Edward Shorter's Dramatic Personae to Volume One (Starting Up) of *An Oral History of Neuropsychopharmacology* (ACNP 2011).

In the same volume (Volume One) there is a brief paragraph on Elkes' historical contributions to neuropsychopharmacology in Thomas A. Ban's Preface to the volume.

In the following the relevant sections from Ban's Foreword, Shorter's *Dramatis Personae* and Ban's Preface are presented.

## FOREWORD

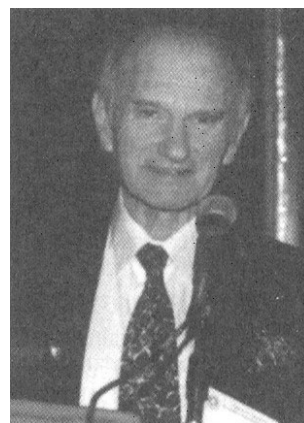
### I. INTRODUCTION

At the XXIst International Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) held in Glasgow, Scotland in 1998, Dr. Joel Elkes was one of the recipients of the CINP-Pfizer Pioneer in Neuropsychopharmacology Award. It was for the first time that this honor was extended to three "exceptional individuals." The other two recipients were Pierre Deniker from France, and Heinz E. Lehmann from Canada.

In this first volume of a CINP series, dedicated to the "pioneers," the selected writings of Joel Elkes are presented. Elkes "made his mark with his visionary approach of linking basic research and clinical psychiatry" (1). By recognizing the importance of neurochemical transmission in the central nervous system far ahead of his peers, and defining what a "neurotransmitter" is (2), he was instrumental in opening the path for the detection of molecular changes responsible for behavioral effects. Furthermore, by adopting "behavioral pharmacology" as a tool for examining psychiatric concepts, he triggered a re-evaluation of the frame of reference of mental illness. In 1966 Elkes wrote (3):

"It is one of the overriding merits of 'behavioral pharmacology' that it is forcing many issues which have lain dormant in the behavioral sciences, and in clinical psychiatry; and that it compels a re-examination of both instruments, and point of references in neurobiology and psychiatry. The subject to be sure, is peculiarly suited to the role. It ranges from behavior to the neural substrate of behavior, from the silent transactions of 'thought,' to the physics, chemistry and mathematics of the cerebral machinery. Its evolution is marked by two mutually complementary processes, proceeding simultaneously. First, the resolution of the area into the disciplines which compound it; and secondly, and more important, the fusion of disciplines, thus defined, into the elements of a new science. A pharmacology preoccupied with tissues and organs is gradually giving way to a pharmacology of the behavior of the total organism; and although old rules obtain, new rules are in the making, and the game itself is assuming strange an unexpected ways."

Elkes, through his professional activities put the behavioral sciences in the service of medicine, and art in the service of healing. With his exceptional ability "to make people aware that their work involves more than the routine drudgery of science, that they are also working on issues of fundamental concern to humanity," Elkes, "can deliver a unique message to that place in the listener's heart where 'meaning' and 'hope' meet" (4).



Dr. Joel Elkes after receiving the CINP-Pfizer Pioneers in Neuropsychopharmacology Award

## II. BIOGRAPHICAL

Joel Elkes was born in Koenigsberg, the capital of eastern Prussia on November 12, 1913. His father, a prestigious physician in nearby Lithuania, and the elected leader of the Kovno ghetto during the German occupation of the country, died in Dachau in October 1943. His mother, the daughter of a moderately prosperous grain merchant in Koenigsberg, survived the holocaust, and died in 1965 in Israel.

Joel spent his first five years in Russia. His father was a medical officer in the Russian army during the first World War and the family was traveling with him and his regiment through the vicissitudes of the Russian revolution. He was about five years old in 1918, when the family settled in Kovno, near Kalvaria, the birthplace of his father.

Joel grew up in Kovno. His parents spoke German at home, and he attended a "gymnasium" (high school) in which every subject was taught in modern Hebrew. Nevertheless, he could write in Lithuanian as a "mature poet," as one of his teachers noted (5). His school was founded by a group of idealists determined to give Jewish children a good education and prepare them for a constructive life in Palestine (Israel). Moshe Schwabe, the head of the school, was a professor of Greek in Germany, his native country. He was to become the rector of the Hebrew University of Jerusalem.

Joel finished high school with high honors. He excelled in literature and biology, but his favorite subject was physics. When recently asked about his early interests he mused and said: "To find out how the world is held together," and "to visualize the forces which keep it together." It was structure, particles, forces, fields, which have fascinated him all through the years (5).

After "Schwabe's Gymnasium" Joel studied in Koenigsberg for a year, to get a matriculation from a German school. It was a challenge to catch up with his peers in German literature and French language, but by the time of graduation he was at the top of his class. It was in the late 1920s, just a few years prior to Hitler's rise to power, and he was the only Jew in the school.

After Koenigsberg, Joel spent four months in Lausanne, Switzerland, attending lectures at the university on elementary biology, embryology, and especially physics -which remained the center of his interest, even after he reached the decision to enter medical school. Then, in October 1930, he left Kovno for England with a letter of recommendation from the British Ambassador to Lithuania, that helped him to get admitted to study medicine at St. Mary's Hospital in London. The dean of the medical school was Sir Charles Wilson, who was to become Lord Moran (Churchill's personal physician), and the faculty included Sir Almroth Wright, who developed the typhus vaccine, Alexander Fleming, who discovered penicillin, and many others, including Aleck Bourne, eminent obstetrician, who was to become his father in-law.

In the mid-1930s Alastair Frazer, a senior lecturer in physiology, invited Joel to work with him in his laboratory. Frazer was studying the absorption of fat from the alimentary canal and was concerned with chylomicrons flooding the circulation from the thoracic duct after a fatty meal. Joel developed a microelectrophoretic cell to study the mobility of chylomicrons in an electric field. His research in physiology led to a paper on the composition of particles seen in normal human blood under ground illumination. It was published in the *Journal of Physiology* in 1939 (6), and its conclusions were incorporated by Starling in his prestigious *Principles of Human Physiology*, before he finished medical school.



In spite of his success in research, the pressures were growing and Joel, on the advice of his counselor, who was no lesser a person than John Bowlby, entered psychoanalysis. It began as a personal analysis, but continued as a training analysis which qualified him some years later for becoming a scientific associate in the Academy of Psychoanalysis (USA).

Joel also had financial difficulties. His earnings from tutoring were insufficient to support him and his sister, who had been left to his care in 1937. He had been cut off from the money he received from his father at the start of the second World War. The financial crisis was resolved with the help of Alastair Frazer, who found him a job in the newly established Transfusion Service, where he met Charmian Bourne, the daughter of his professor, who was to become his first wife.

Joel graduated from medicine in 1941, and subsequently worked as a rotating intern in orthopedic surgery, ophthalmology and internal medicine. He was enjoying clinical work and thinking of taking the necessary examinations for opening an office in London to practice medicine. This did not happen. Instead, he accepted an invitation from Alastair Frazer to join him as his research assistant. Frazer had just been appointed chairman of the Department of Pharmacology at the University of Birmingham.

On the 18th of December, 1944, Joel married Charmian Bourne, who was in general practice at the time. Their first and only child, Anna, was born on the 12th of April 1946. By that time he was in charge of a mental disease research unit in Frazer's department. To further his knowledge in psychiatry he spent about a year in the United States (as a Smith Kline and French, and Fulbright Fellow), working in Samuel Wortis' Institute at New York University, at the Pratt Diagnostic Center, and at Norwich State Hospital in Connecticut.

Upon return to Birmingham in 1951, he was appointed Head of the first Department of Experimental Psychiatry in the world. The department embodied Joel's vision of bridging basic research and clinical psychiatry. He became professor of psychiatry at a time when there were only three other chairs of psychiatry in the United Kingdom (4). The department received support from the Rockefeller Foundation and from the Medical Research Council of England. In spite of his lack of formal training in psychiatry Joel became a Charter Fellow of the Royal College of Psychiatrists of Great Britain.

In 1957 Joel moved with his family to the United States. He was invited by Seymour Kety and Robert Cohen, to set up and direct the Clinical Neuropharmacological Research Center of the National Institute of Mental Health (NIMH) at St. Elizabeths Hospital. Subsequently, from 1963 to 1974, he was Chairman of the Department of Psychiatry at Johns Hopkins University, and Director of the Phipps Psychiatric Clinic, succeeding Seymour Kety. He was elected Distinguished Service Professor at Hopkins at the time of his retirement. The end of his tenure were marred by his divorce from Charmian.

During the 1970s and 1980s Joel continued with his professional activities; first as Samuel McLaughlin Professor at McMaster University (Hamilton, Ontario, Canada) and, then at the University of Louisville (Kentucky, USA). He married Josephine Rhodes, and while living in Canada he returned to painting, a long standing hobby. His summer home in Prince Edward Island, Canada, offered plenty of opportunity for this. It was also in their summer home on Prince Edward Island he completed his memoir on his father, Elkhanan Elkes (7).

While chairing departments and directing clinics and laboratories, Joel remained faithful to his long standing heritage of "Schwabe's Gymnasium." He played an important role in founding the Israel Center for Psychobiology, and developing it to become the National Institute of Psychobiology of Israel. He was Founding Director of this cooperative, inter-institutional,

and deeply influential body for the support of the neurosciences and psychobiology in the country. He also served as Trustee of both, the Hebrew University of Jerusalem and Haifa University, where, in 1982, he was instrumental in convening a working conference on "Mankind 2000." Around his seventieth birthday, in 1984, an international symposium on psychopharmacology was held in his honor at the University of Louisville. Its theme, significantly, was "The Visible Brain." Visualizing by modern methods the regional neurochemistry of the brain had been Joel's preoccupation for many years. Four years later, in 1988, the Neuroscience Laboratories of the Department of Psychiatry and Behavioral Sciences at Johns Hopkins University were named after him. In 1989, together with Abba Eban, Zubin Mehta, and Senator Inouye, he received an honorary degree from the Hebrew University.

On the 30th of October, 1989, Joel spoke for the first time of his father, Dr. Elkhanan Elkes to an audience in Leicester University in the UK. Also in 1989, Joel was elected Fellow and Senior Scholar of the Fetzer Institute in Kalamazoo, Michigan.

In the early 1990s Joel was still active in Louisville. In 1992, he delivered a Distinguished Psychiatrist Lecture at the Annual Meeting of the American Psychiatric Association in New Orleans (8), and in the same year, at an international meeting he was the recipient of the International Hans Selye Award.

From the mid 1990s, Joel spent summers at the Fetzer Institute in a cottage which bears his name, and the winters in his home in Sarasota (Florida) where he spends some of his time painting. Josephine died in 1999. Today, in his late eighties, Joel moves and acts, thinks and speaks like a much younger man. He is an accomplished artist. His paintings are in watercolor and charcoal.



Past Presidents' and Congress Organizers' Luncheon. Tuesday, July 14, 1998. XXIth CINP Congress, Glasgow, Scotland. Front row (left to right): Leo Hollister, Julien Mendlewicz, Heinz Lehmann, Joel Elkes, Alec Coppen, William Bunney. Back row: Hanns Hippus, Giorgio Racagni, Oakley Ray, Claude de Montigny, Eugene Paykel, Gregor Laakmann, Tomoji Yanagita.

### III. PROFESSIONAL ACTIVITIES

Joel Elkes' professional activities, while broad in range, have shown an inner consistency and durability over the years. Seen in retrospect, most of the themes recur and are interwoven in his writings, and are reflected in the planning of the working environments of the institutions which he founded and directed. Some ideas, while formulated early, had to await their time; others were taken up by students and collaborators and developed in new environments.

Elkes has consistently tried to maintain a transdisciplinary conversation in the groups he led. The science of which he is recognized founder – neuropsychopharmacology – made this a mandatory requirement from its earliest beginnings. For like few fields, it ranges from neurochemistry and cellular neurobiology to behavior and subjective experience, providing a conceptual link between brain, mind, behavior, and the social field; and between the neurosciences and psychiatry. He pointed out these connections, including the susceptibility of drug effects to social cues, in several papers, including the first World Health Organization (WHO) "Technical Report" that he wrote (*Ataractic and Hallucinogenic Drugs in Psychiatry*) (8). Psychopharmacology has provided him with a template, and early guideposts, to human biology, his real field of interest.

Well over 40 years passed since the publication of the WHO report, and during these years Elkes has become increasingly involved with the body's "inner pharmacy," and with the "autopharmacology" of the regulatory processes of the body. By the 1970s he felt that the neurosciences, including neurochemistry, neuroendocrinology, neuroimmunology, and cognitive psychology were ripe for quantitative inquiries into the more sparsely described states of health, wellbeing, successful coping, and personal competence; and by the 1980s he became keenly aware of the need for translation of this new knowledge for the benefit of the health professions and the general public, i.e., of the need for new educational experiments to bring this new knowledge into the mainstream of medical education and clinical practice.

Elkes' professional interests can be divided into five closely connected areas. In the following, his activities in these five areas are briefly reviewed.

#### *III.1 Neurochemistry and psychopharmacology*

Elkes began his scientific life in physical chemistry (9) and crystallography (10). With his first Ph.D. student, J. B. Finean, he was first to present, in the late 1940s, X-ray diffraction diagrams of the living myelin sheet (10, 11). This led him, by way of neuropharmacology and neurochemistry into work on the influence of drugs on electrochemical events in the brain, yielding ultimately to the field which later became known as "psychopharmacology." He tried to develop psychopharmacology with the help of devoted colleagues, starting in the animal laboratory but rapidly extending into the clinic. In recognition of his activities, the "Department of Experimental Psychiatry" was created for him by the University of Birmingham in the early 1950s. It comprised experimental animal laboratories and a strong clinical arm, the "Uffculme Clinic," with an outpatient facility, a day hospital, a 40 bed unit, a patient's club, and a domiciliary visiting service (12).

It was during his "Birmingham period," that Elkes developed his concepts of the operation of regional chemical fields within the brain, and the existence of families of neuroregulatory compounds which, between them, govern and modulate states of excitation and inhibition. It was also in Birmingham that he was mapping the cholinesterases in various areas of the brain,

and observing the effect of the inhibition of the cholinesterase enzyme on the emergence of various inborn reflexes (13, 14); in collaboration with Philip Bradley he studied the effects of physostigmine, atropine, hyoscyamine, amphetamine, and lysergic acid diethylamide on the electrical activity of the brain in conscious animal with the employment of a newly developed electrode technique (15); and in collaboration with Charmian Elkes, his late first wife, he was exploring the effects of amobarbital, amphetamine, and mephenesin on catatonic stupor (16). It was also with Charmian Elkes that he conducted the first blind controlled clinical trial of chlorpromazine in chronic psychotic patients (17).

Elkes' research in the Department of Experimental Psychiatry attracted attention in the United States and, as indicated before, in 1957 he was invited to the United States to create NIMH's Clinical Neuropharmacology Research Center (CNRC) in the William A. White Building at St. Elizabeths Hospital. By the late 1950s research in the CNRC ranged from the micropipette studies of Salmoiraghi and Bloom, the early dopamine studies of Weil-Malherbe, and the tryptamine studies of Szara, to the clinical drug trials of Freyhan, Hordern and Lofft. Within a period of merely six years Elkes succeeded in contributing to NIMH's influential, intramural research program in neuroscience.

Elkes was also active in developing the necessary means for communication in the new field, i.e., platforms (meetings) and organs (journals). As early as in the mid-1950s he organized, in collaboration with Drs. S. Kety, H. Waelsch, J. Folch, D. Richter and G.W. Harris, the first International Neurochemical Symposium in Oxford, followed by a symposium on regional neurochemistry. In 1957 he was the convener of the first working group of the World Health Organization (WHO) on psychotropic drugs, and represented neuropharmacology, together with the Nobel Laureate, Daniel Bovet, at the founding meeting of the International Brain Research Organization (IBRO). He also participated in 1960 in the writing of the constitution of IBRO; in the organization of the first congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP); and in the founding of the American College of Neuropsychopharmacology (ACNP). In his memorable lecture as Founding President of the ACNP he defined the place of neuropsychopharmacology and gave an identity to the "new science" by saying:

"It is not uncommon for any one of us to be told that Psychopharmacology is not a science, and that it would do well to emulate the precision of older and more established disciplines. Such statements betray a lack of understanding for the special demands made by Psychopharmacology upon the fields which compound it. For my own part, I draw comfort and firm conviction from the history of our group. For I know of no other branch of science which, like a good plough on a spring day, has tilled as many areas in neurobiology. To have, in a mere decade, questioned the concept of synaptic transmission in the central nervous system; to have emphasized compartmentalization and regionalization of chemical process in the unit cell and in the brain; to have focussed on the interaction of hormone and chemical process within the brain; to have given us tools for the study of the chemical basis of learning and temporary connection formation; to have emphasized the dependence of pharmacological response on its situational and social setting; to have compelled a hard look at the semantics of psychiatric diagnosis, description and communication; to have resuscitated that oldest of old remedies, the placebo response, for careful scrutiny; to have provided potential methods for the study of language in relation to the functional state of the brain; and to have encouraged the Biochemist, Physiologist, Psychologist, Clinician, and the Mathematician and Communication Engineer to join forces at bench level, is no mean achievement for a young science. That a chemical text should carry the imprint of ex-

perience, and partake in its growth, in no way invalidates study of symbols, and the rules among symbols, which keep us going, changing, evolving, and human. Thus, though moving cautiously, psycho~pharmacology is still protesting; yet in so doing it is, for the first time, compelling the physical and chemical sciences to look behavior in the face, and thus enriching both these sciences and behavior. If there be discomfiture in this encounter, it is hardly surprising; for it is in this discomfiture that there may well lie the germ of a new science.” (See full text in Part One, Chapter 4).

An annual international award for distinguished work in psychopharmacology carries his name in the college.

Elkes was one of the founding editors of two major journals: *Psychopharmacologia* (now *Journal of Psychopharmacology*), and *Journal of Psychiatric Research*.

In the early 1960s he wrote the section on “Behavioral Pharmacology in Relation to Psychiatry” for Springer’s *International Handbook of Psychiatry*. (See full text in Part Four, Chapter 15.) In this much quoted paper Elkes argues that pharmacology has the role of a conduit to psychobiology, an attitude he later also reflected in his closing chapter of Clark and del Giudice’s *Principles of Psychopharmacology*. (See full text in Part Six, Chapter 17.)

In 1963 Elkes moved from the NIMH to Johns Hopkins University to become Chairman of the Department of Psychiatry. As Psychiatrist-in-Chief, and Henry Phipps Professor of Psychiatry, he supported his residents and fellows to develop the necessary skills to further experimental and clinical neuropsychopharmacologic research; and as Chairman of the department, he created research laboratories in psychopharmacology, neuroendocrinology, behavioral medicine, and in the clinical sciences.

### *III.2 Clinical psychiatry and behavioral medicine*

Elkes believes that modern psychiatry provides a natural bridge between the behavioral sciences and medicine as a whole, including preventive medicine, and to facilitate the use of this natural bridge he changed the name of his department at Johns Hopkins from “Psychiatry” to “Psychiatry and Behavioral Sciences.” It was one of the first, if not the first departments so to change its name in the world. The behavioral sciences thus represented a counterpoint to his interests in the neurosciences and neurobiology. What later was to become known as “behavioral medicine” grew at Hopkins under his direction as an organic continuation through the work of Curt Richter, Horsley Gantt and Jerome Frank in the great tradition in psychobiology, pioneered by Adolf Meyer. During his tenure at Johns Hopkins Elkes developed a program, rather than a center for “Behavioral Medicine.” He also founded the first society for “Biofeedback and Self Regulation” in the USA.

To continue and expand what he started at Johns Hopkins, he developed at McMaster, a major program of “Brain and Behavior,” and a “Division of Behavioral Medicine.” He did the same in Louisville where he created with his second wife, Josephine Rhodes and some other colleagues, the Genesis Center for the management of chronic illness. He served as director of the program which was engaged in research on the effect of group counseling in chronic disease, particularly in rheumatoid arthritis, pain and cancer.

### *III.3 Study of subjective phenomena: the role of language in psychiatry*

Elkes has had a central interest in the subject of personal awareness and the transforms of mental life, including the play of phantasy and imagination in daily living. The concepts of psychopharmacology led him to source, to physiology to the way the brain “does it naturally,” without the aid of chemical prostheses. Awareness, self-observation, focussing on inner speech, became to him a valid area of inquiry. As a student he was deeply interested in states of consciousness, meditation, autoregulation, and also in the interaction of mental events with muscle activity, and bodily function. These subjects led him to an interest in the limitations of language in the description of subjective, behaviorally silent states of mind.

When invited to speak on psychopharmacology in his Harvey Lecture, delivered in 1961, he chose instead to speak on “Subjective and Objective Observations in Psychiatry” and the role of language in the description of subjective phenomena. (See full text in Part Eight, Chapter 24). He spoke in his presentation on the serial and parallel processing of information by the brain. He also argued for the establishment of “Inner Space Laboratories.” Similarly, he examined information processing in relation to levels of neuronal organization in schizophrenia. (See full text in Part Five, Chapter 16). In his Salmon Lectures, delivered in 1963 he spoke on “Chemistry, Awareness, and the Imagination.” (See abstracts in Part Eight, Chapters 22 and 23). And in his Bronowski Memorial Lecture, delivered in 1978, he examined the role of “Awareness” in daily life. (See Part Eight, Chapter 25). Elkes regards the day as an opportunity for experiment and the body/mind as an ever present portable laboratory, accessible to anyone who wishes to use it. Such ideas may seem a little strange within the traditional medical framework; yet, there is a mounting body of evidence connecting imagery and states of consciousness with somatic function. He believes that the methods for somatic, (including biochemical and immunological) monitoring of mental events have now reached a degree of refinement compatible with good experimental design.

### *III.4 Social psychiatry and community planning*

Stimulated by “The Peckham Experiment,” an experimental health center in a working-class neighborhood in London in the late 1930s. (See more details in Part Nine, Chapter 27), Elkes organized his early treatment center, the Uffculme Clinic, housed in the former Cadbury Mansion in Birmingham, in a manner which provided a prototype of his idea of a comprehensive psychiatric care facility. He tried to develop the same model when he moved to the United States. At the same time he also emphasized the use of mental health principles in community planning. This found expression for the first time in 1966, in a comprehensive plan submitted to the Secretary of Health of Maryland, on the application of behavioral sciences to the planning of neighborhoods. The concept of a “healing community,” he formulated in this document won him a citation from the Governor of the State.

To meet the needs of “behavioral medicine” Elkes’ first wife, Charmian embarked upon a training program for “mature woman.” The “Phipps Ladies,” as the trainees became known, were rigorously selected for their stability, maturity, empathy, and interpersonal skills.

When an opportunity arose for the planning of a completely new city, Columbia, Maryland, by the Rouse Company, Elkes was instrumental in designing and creating a prepaid, low-fee mental health service, functioning alongside the major primary care specialties – medicine, pediatrics, and obstetrics and gynecology. (See more details in Part Nine, Chapters

28 and 29). While serving on the advisory council for the planning of the new city, he developed, in collaboration with colleagues, a survey of human resources for the community.

In the same vein, at the University of Louisville, Elkes created the “Wellness Forum,” a community resource dedicated to educating the corporate sector, the professions, and the public in matters of “health maintenance,” “health enhancement,” and “self care.” It was a consortium, sponsored by the county medical society, the university, the chamber of commerce, and other civic organizations, to promote the concepts of preventive health care, and long term health research in the community. As the honorary president of the forum, and a member of the health advisory council of the State, Elkes was actively engaged in furthering the cause of a State funded center for health promotion and disease prevention in Kentucky during the 1980s.

### *III.5 Humanizing medical education: the behavioral sciences in the service of medicine*

All through his professional life Elkes has had an abiding interest in what is conventionally referred to as the “mind/body connection,” and in the emerging concepts of psychosomatic medicine. He acted on his convictions by reading widely in the field and getting personal exposure to the phenomena of yoga, relaxation, meditation, and imagery. While engaged in his studies in physical chemistry, he was impressed by the restorative powers of these techniques, and incorporated some very elementary exercises in his daily life during the stressful years of the second World War.

Elkes has also been interested in Hans Selye’s concept of “stress” since the time of its inception in the late 1930s. He knew Selye, and assisted him in founding both, his International and American Stress Institute. He was founding president of the latter.

Elkes was trying to incorporate some concepts and techniques of stress management into the practice of his clinics, and the education of his students, in Birmingham; however, the first real opportunity to do so presented itself at Johns Hopkins, where he succeeded in introducing an “introductory course in behavioral sciences” for medical students. The core message of the course was to connect the behavioral sciences to medicine as a whole, i.e., not merely to psychiatry, and provide each student an opportunity to meet him/herself, and use his/her own “body/mind” thoughtfully in daily living. (See more details in Part Seven, Chapter 19). The course was built around theories of Human Development, Human Learning, Human Communication, and the operation of the “Social Field.” A common thread running through the course was “behavioral biology,” and some emerging concepts of regional chemical regulation (and self regulation) of the brain. The course was one of the first attempts to make sense of the biological origins and correlates of symbolic life, and to convey to the student a deep respect for personal awareness, self observation, and the realities of “psychobiology.”

Elkes’ experience at Hopkins made him aware of the great stresses undergone by students in the course of their training, and when the opportunity at the University of Louisville arose, he created in collaboration with Leah Dickstein a “Health Awareness Program” for incoming medical students. The objective of the program was the correction of the lack of training in preventive medicine, and of the inattention-by-default to the personal wellbeing of students in medical institutions. The program was based on the assumption that “other-care” is best begun with “self-care;” and that “awareness of self and others” is at the very heart of humane medical practice; and on the belief that if awareness is coupled with training in simple life

skills and lifestyle principles – all based on common sense; it may go some way to help future physicians cultivate the same skills in their patients.

The “connection course” was another elective he introduced. It was a collaborative effort between the Division of Attitudinal and Behavioral Medicine and the Department of Family Practice at the University of Louisville. The purpose of the course was to focus attention on the reality of mind/body interaction in the practice of medicine. The course was centered on chronic illness, and involved visits to patients’ homes.

Elkes succeeded also in introducing a Program in the arts in medicine. He observed that arts can reach areas of emotional life inaccessible to traditional approaches; recognised that they can move beneath and beyond words; and believed that art therapies, at their best, are deeply restorative and healing. The implementation of this program was part of his overall effort to humanize medical education. His aim was to bring about a meeting of two cultures – the culture of the arts and of the medical sciences. (See more details in Part Twelve.)

Finally, before leaving almost six decades of professional activities, Elkes developed a proposal for the creation of a center for comprehensive medicine and health enhancement which, by widening the concept of health to include mental, social and spiritual well-being, would create a climate that could play a significant part in changing the prevailing culture of medical institutions.

#### **IV. IMPACT THROUGH TRAINING OF PROFESSIONALS**

The impact of Elkes’ professional activities on the development of neuropsychopharmacology through training of professionals is unparalleled. The list of the people who passed through his laboratories reads like a Who’s Who of American Psychopharmacology (4). At the University of Birmingham he drew together a cohort of researchers, including Philip Bradley, Brian Key, Michael Chance, Charmian Elkes, and Willy Mayer-Gross, with seminal contributions to the establishment of the field. At the NIMH in Washington he started with a secretary (Anne Gibson) and by the time he left for Johns Hopkins he had a large staff of prominent researchers and clinicians including Floyd Bloom, Max Hamilton, Eliot Hearst, Anthony Hordern, John Lofft, Richard Michael, Shepherd Kellam, G.C. Salmoiraghi, Steven Szara, Neil Waldrop, Hans Weil-Malherbe, Harold Weiner, and many others (9). And while he was chairman at Johns Hopkins, Solomon Snyder began with his pathbreaking neurochemical studies while still a resident in psychiatry, Joe Brady built primate-laboratories for his far-reaching program in behavioral biology, Ross Baldessarini began with his career in clinical psychopharmacology, and “Uhli” Uhlenhuth, Lino Covi, and Len Derogatis developed their rating scales and engaged in important outpatient studies.

During his working years Elkes has contributed to the development of some 35 to 40 investigators who have assumed prominent, and in some instances leading positions. The span of activities of these investigators has been wide, ranging from cellular biology (Floyd Bloom and Solomon Snyder), clinical psychiatry and psychology (Freyhan, Kellam and Weingartner), clinical psychopharmacology (Baldessarini and Van Kammen), to the study of the states of consciousness (Stanislav Grof). Among Elkes’ former associates there are two past presidents of the prestigious Society of Neuroscience (Bloom and Snyder), three deans of medical schools (De Vaul, Freeman and Knorr), and some fourteen chairman and/or institute and program directors, including the chairman of psychiatry at Harvard (Coyle), and the director of Research of the Mayo Clinic at Jacksonville (Richelson).



## V. THE CONTENT OF THIS BOOK

This book reflects an attitude to Psychopharmacology. Its content is not restricted to a collection of Joel Elkes' papers in neuropsychopharmacology, but includes also his contributions to other areas in the behavioral sciences and some of his personal reflections.

Joel Elkes connects. His interests range wide – from the molecular building blocks of the brain to social behavior. In each area his inquisitive spirit poses questions; questions which he continues to ask even if answers are not readily forthcoming.

It is the intention of this editor to present Joel Elkes, the man. It took long arguments into the night to convince him to allow the inclusion of non-technical material, and his Art. For that reason, the material is, at times, repetitious, and references are missing. However, all relevant references are comprised in the papers quoted.

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Thomas A. Ban  
Editor

## **2.2 From Edward Shorter's *Dramatis Personae* in Volume One of *An Oral History of Neuropsychopharmacology***

Born in 1913 in Königsberg, Germany, the son of a distinguished physician, *Joel Elkes* grew up in nearby Kovno, Lithuania, filled with the spirit of science and the love of physics. In 1930, at seventeen, he left Kovno to study medicine at St. Mary's Hospital Medical School in London, his course of study broken by intermittent financial difficulties – these were not easy times for Jews in Central Europe. He graduated in medicine in 1941 and, still animated by the desire to combine physics and biochemistry (though the term had not yet been invented), he accepted in 1942 a fellowship in pharmacology at the University of Birmingham. Elkes later insisted that his interest in psychiatry at the time was minimal, yet in 1937 he began training in psychoanalysis (completing a diploma in 1955 in Washington DC). At Birmingham, Elkes plunged into the study of lipoproteins and ended up working on myelin in the central nervous system. This was the beginning of his efforts to establish a physical, neurochemical basis for psychiatric phenomena.

After a year in the US as a Fulbright Fellow, in 1951 Elkes returned to Birmingham and became the founding director of the Department of Experimental Psychiatry, which had the mission of linking the University's basic science laboratories to the behavior of patients in the psychiatric wards of the University of Birmingham Hospitals. Supported by the Rockefeller Foundation and the Medical Research Council of England, they had at their disposition experimental animal laboratories plus a forty-patient ward in the former Cadbury mansion in Birmingham that they called the "Uffculme Clinic." This seems to have been the first experimental facility in the world dedicated to psychiatry and psychopharmacology. As Elkes said in the *University of Birmingham Gazette* in 1955, "The laboratory work of the Department rests on the assumption that the various manifestations of gross mental disorder and milder dysfunction have their counterpart in a disturbed physiology of the brain, and that the study of the chemistry, the cellular constitution, and the electrical activity of the brain may contribute to an understanding of its function as the highest integrating organ."

In his interview in this volume, Elkes recalls the excitement as they began to discover the specificity of drug action. Although they were not the first to document the therapeutic effect of the barbiturates on catatonic stupor, they did note that unexpectedly, amphetamine deepened it. At Winson Green Hospital in Birmingham, Elkes and his wife Charmian Elkes, who was the chief investigator, conducted one of the earliest controlled trials of chlorpromazine, publishing the results in the *British Medical Journal* in 1954. “This is one of the milestones in psychopharmacology”, said interviewer Fridolin Sulser.

In 1957 Elkes left Birmingham for the NIMH in Bethesda, Maryland. “The field was developing very fast in the United States, and I wanted to be part of it,” he said in the interview. He established the Behavioral and Clinical Studies Center at St. Elizabeth’s Hospital in Washington DC; Elkes also directed its homologue at NIMH, the Clinical Neuropharmacology Research Center. At NIMH, Elkes’ interest in regional neurochemistry intensified -- he considered this kind of research among his most important life accomplishments – and in 1961 he and Seymour Kety published the proceedings of an agenda-setting conference on the subject. In his subsequent tenure as chair of psychiatry at Johns Hopkins University, Elkes inspired an entire generation of American biological psychiatrists. “My job was to cultivate talent,” he said. Eugene Paykel later referred to Elkes as “the father of neuropsychopharmacology.”

### **2.3 From Thomas A. Ban's Preface to Volume One of An Oral History of Neuropsychopharmacology**

At the time that understanding about signal transduction in the brain was shifting from a purely electrical to a chemically mediated event, *Joel Elkes* developed his concepts of the operation of regional chemical fields within the brain, and the existence of families of neuroregulatory compounds which, between them govern and modulate states of excitation and inhibition.

Elkes conducted the first blind-controlled cross-over clinical trial with chlorpromazine in chronic psychotic patients; explored the effects of amobarbital, amphetamine and mephenesine on catatonic stupor; studied the effects of centrally acting drugs on the electrical activity of the brain in conscious animals; mapped the cholinesterases, responsible for the formation and breakdown of acetylcholine in various areas of the central nervous system; and observed the effect of the inhibition of the cholinesterase enzyme on the emergence of various inborn reflexes. Acetylcholine was the first neurotransmitter identified and also the first neurotransmitter with its effect of mental, integrative functions, such as consciousness, memory characterized.

### **3 AUTOBIOGRAPHIC ACCOUNT**

An autobiographic account of Joel Elkes' professional activities in the 1940s and '50s is presented in Volume One (The Rise of Psychopharmacology) of The History of Psychopharmacology and the CINP, As Told in Autobiography, with the title: Towards footings of a science: Personal beginning in psychopharmacology in the forties and fifties (Animula 1998; CINP 2010).

In the following this chapter is reproduced in full.

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## **TOWARDS FOOTINGS OF A SCIENCE: PERSONAL BEGINNINGS IN PSYCHOPHARMACOLOGY IN THE FORTIES AND FIFTIES**

**Joel Elkes**

### **A PROGRAM ON “DRUGS AND THE MIND” – EXPERIMENTAL PSYCHIATRY IN BIRMINGHAM, ENGLAND**

The inverted telescope of recollection is apt to diminish and obscure persons and events. However, in this instance, they remain clear, distinct, and warming to recall. I have referred to them more extensively in a recent invited address (1). It also carries a fuller bibliography.

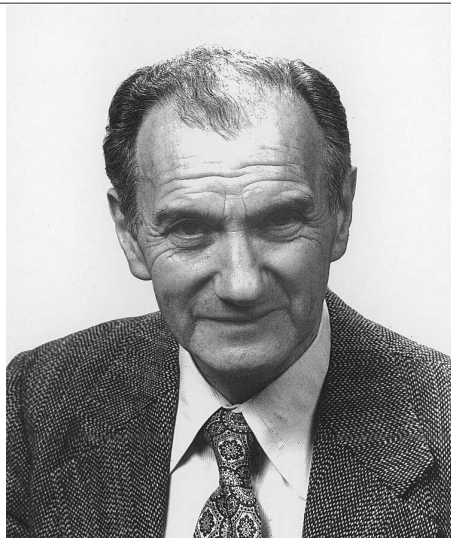
The dialectic between Psychiatry and Molecules began quite early in my life. As a medical student at St. Mary’s Hospital, London, in the thirties, I was deeply attracted to psychiatry. However, the excellent lectures and demonstrations in the local mental hospital left me bewildered, curious and hungry, and groping for a physiology and chemistry which at the time did not exist. Immunology was very strong at St. Mary’s (where, some ten years later, Fleming discovered penicillin). So, one read wildly in immunology, particularly on Paul Ehrlich’s ideas about cell surfaces, receptor configuration, specificity, side-chains (“Seitenketten”) and the like. Soon, the lipoprotein structure of cell membranes became a consuming interest. I spent two gorgeous summers in the Department of Colloid Science at Cambridge under Sir Eric Rideal, spreading monomolecular films and reading on crystallography. Getting into microstructures (membranes, organelles) became a persistent visual game. I did not know it then, but I was heading into pharmacology.

The opportunity came in 1941, when I accompanied my erstwhile chief and friend Alastair Frazer to Birmingham to help him found what, in retrospect, was to become a major department of pharmacology. Psychiatry was always beckoning in the background; but in those days, there were few bridges leading from cell biology to psychiatry, and it was not easy to convince university authorities that “Mental Disease Research” (as it was called) was a worthwhile enterprise.

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Joel Elkes is Distinguished Service Professor Emeritus at Johns Hopkins University, Baltimore, and Distinguished University Professor Emeritus in the University of Louisville. At present, he is Senior Scholar in Residence at the Fetzer Institute, Kalamazoo, Michigan. He founded the Department of Experimental Psychiatry in the University of Birmingham, England, in 1951, and subsequently (1957- 63) served as Director of the Clinical Neuropharmacology Research Center, NIMH, Washington, D.C. He served as Psychiatrist-in-Chief and Director of the Department at Johns Hopkins between 1963 and 1975. After his retirement from Hopkins, he helped to create a program in Behavioural Medicine at McMaster University, Hamilton, Ontario, Canada, (1976-1981) and continued in cognate programs in the Department of Psychiatry, University of Louisville (1981-1994). In 1961, he was elected the first President of the American College of Neuropsychopharmacology.

Elkes was elected a fellow of the CINP in 1960. He presented a paper entitled “On the relation of drug-induced mental changes to the schizophrenias” at the 1st Congress



Joel Elkes



The leading laboratories were small, not very well equipped, and usually functioned outside universities, being mostly supported by local hospital boards. Yet, in retrospect, I was most fortunate. In Birmingham, I found acceptance of my interest in the chemistry of the brain, and, more importantly, while teaching conventional pharmacology I was allowed to stray. My colleagues and I strayed into the study of the cholinesterases, and the very powerful and specific anticholinesterases. We began mapping the distribution of these enzymes in the brain, noting their unevenness in the hope of finding a clue to the action of hypnotics. I was also fortunate in another respect. Tracking back to my days in physical chemistry, Bryan Finean (as my first PhD student) engaged in X-ray diffraction studies of living myelin, demonstrating clearly its ordered lamellar, paracrystalline structure (2). After two years of work in this field I found myself anchored. Neurochemistry extended its powerful pull, with psychiatry moving ever closer. At about this time (1945), another pivotal event took place. A small unit of "Mental Disease Research," loosely administered from the Dean's Office, became available. It fell under the aegis of the Department of Pharmacology, through the retirement of its director, Dr. A. Pickworth. I was put in charge of two rooms in the medical school. There was also some seed money. An enormous step in my life had been taken; I knew I was in biological psychiatry for good.

I began to read avidly, to train myself by seeing patients in the local mental hospital (the Winson Green Mental Hospital), and to familiarize myself with the drug treatments then available. The old reliable triad – bromine, chloral hydrate, and the barbiturates – was ever present, and the anti-epileptic drugs were coming into their own at the periphery. There was, of course, also insulin coma and ECT. Vast questions beckoned everywhere: I felt like a naturalist advancing into a strange continent. Deeply moved by what I saw and heard in the ward, I found myself discussing my bewilderment with Charmian, my late first wife, who was in general practice at the time. We talked into the night, pulled by the same curiosity. One day, after a meeting in London, we came upon reports on the effects of drugs on catatonic schizophrenic stupor. The syndrome was not uncommon in our mental hospital, and we were struck by the

combination of mask-like rigidity, withdrawal, and cyanosis of the limbs. Quietly, Charmian suggested that we plan a study.

When we proposed this to Dr. J.J. O'Reilly, superintendent at Winson Green Mental Hospital (The Birmingham City Mental Hospital – now All Saints Hospital), he readily agreed and remained our supporter and friend in years to come.

Dr. O'Reilly put a small research room at our disposal and allowed us to choose patients, using our criteria; he also gave us nursing help. We used homemade gadgetry to measure "muscle tone" (i.e., rigidity) and foot temperature by thermocouple, and we also developed our own rating scales to measure change. The study taught us the enormous value of working in a realistic mental hospital setting. Sodium amytal, administered in full hypnotic doses intravenously, led to a paradoxical awakening of patients from catatonic stupor, a relaxation of muscle tone, and arise in foot temperature. The effect of amphetamine was equally paradoxical. It led to the deepening of the stupor, an increase in muscle rigidity, and a deepening cyanosis. We also tried mephenesin, which had been shown by Frank Berger to be a powerful spinal internuncial neuron blocking agent and, through his prescient insights, later led to meprobamate and the whole family of anxiolytics. When tested in catatonic schizophrenic stupor, mephenesin produced marked muscle relaxation. There was, however, little effect on psychomotor response or peripheral temperature. The ability of patients to draw – for ten minutes, without prompting – while under the influence of drugs proved particularly interesting. Amytal markedly increased this ability, and amphetamine inhibited it. The experiments which we reported later (3) thus suggested *selectivity* in the action of drugs on catatonic stupor and raised the question of the relation of hyperarousal to catatonic withdrawal and, possibly, schizophrenia. Most important, however, these experiments established – at a tangible and a conceptual level – the need of working in parallel. The laboratory and the ward became ends of a continuum of related activities. I began to think of this continuum as *experimental psychiatry*.

At that time, then, there were two anchoring points for our work: neurochemistry, at the bench level, and human behaviour, as influenced by drugs. There was nothing in between, no indicator that could relate the effects of drugs on the brain to behaviour. I began to hunt again. The EEG was at that time coming into its own. Hill and Pond were publishing on the dysrhythmias, and Grey Walter and Gastaut were, in their own idiom, trying to relate functional states in man to EEG activity. And across the water there beckoned the great papers of Herbert Jasper and Wilder Penfield. I plumbed for the effect of drugs on the electrical activity of the brain in the conscious animal. There were very few data available in those days – except, a little later, those of Abraham Wikler and of James Toman's review (4). I obviously could not do it alone, and again, I was in the market for an associate.

I cannot recall now who told Philip Bradley about me or me about Philip Bradley, but I remember clearly his coming to my office and telling me of his experience and his interests. He





had been trained in zoology and had carried out microelectrode studies in insects. He seemed interested in the problem, and a salary was available. So, after some consultation with Dr. Grey Walter, arrangements were made for him to spend some time with Walter to learn EEG techniques and then set up his own laboratory in the second of the two rooms of "Mental Diseases Research." This was duly done, and in 1948, Philip was working alongside us, developing his pioneering technique for recording electrical activity in conscious cats, a procedure that in those days (the days of sulfonamides – not penicillin) was quite a trick. The work proceeded well, and quickly established reference points for a pharmacology of the brain, inasmuch as it relates to behaviour. I still treasure a copy of Philip's thesis completed in October 1952 (5). It was a joy to see the clear and unambiguous effects of physostigmine, atropine, hyoscyamine, and amphetamine (and later, LSD-25) on the electrical activity of the brain in relation to behaviour. It was also particularly satisfying to find how these drugs grouped themselves in terms of their dependence on midbrain structures, and how information arriving at that time from Morruzzi and Magoun's (6) studies could be related to our own findings. There gradually emerged (and this was my own view) a concept of the presence of *families* of compounds that had arisen in the brain, in the course of chemical evolution. These compounds seemed chemically related to powerful neurohumoral transmitters familiar to us at the periphery. Three types of receptors, centering around members of the cholinester, the catecholamine, and later the indole family, were proposed (7, 8). Implicit in this concept of families of compounds was the notion of small regional *chemical fields* and of the interaction between molecules governing the gating, storage, and flow in self-exciting neural loops.

As we wrote at the time (9):

It is likely that neurons possessing slight but definite difference in enzyme constitution may be unevenly distributed in topographically close, or widely separated areas in the central nervous system; these differences probably extend to the finest level of histological organization.... It would perhaps be permissible to speak of the operation of chemical fields in these regions. The agents in question may be either identical with or, more likely, derived from neuro-effector substances familiar to us at the periphery. Their number is probably small, but their influence upon integrative action of higher nervous activity may be profound. The basic states of consciousness may well be determined by variations in the local concentration of these agents.

It gives me special satisfaction to reflect on Philip Bradley's subsequent illustrious career and the influence he has exerted on the course of Neuropsychopharmacology in Europe and the world.

The third area to occupy us in those years concerned hallucinogenic drugs, which, from time to time, had been noted in literature. We began to read about them and formed a small discussion group to explore the possible relation of endogenously-produced hallucinogenic metabolites to schizophrenia. Hofmann's historic report to Stoll was written on April 22, 1943, and Stoll's paper on LSD-25 appeared in 1947 (10). We were immediately struck by the very low dose level, suggesting a specificity of very high order. Our own work in cats and a small number of human volunteers (of whom I was the first), using a single small dose (half a microgram per kilo) led us to conclude, later, that LSD-25 was acting on a serotonin-mediated receptor, peculiarly related to the afferent system (possibly the medial collaterals) (8) and exerting a selective inhibitory role on the organization of sensory information and the serial organization of information in time.

Thus, by about 1949-1950, three elements were in place in our small unit in Birmingham. There was a representation of neurochemistry; a laboratory for the study of electrical activity of the brain in the conscious animal, and there was Charmian's clinical investigation in the mental hospital. A *continuum* was in place. In our presentations and applications for funding, we referred to our program as a program of "Drugs and the Mind."

It is only fair to say that not everybody was friendly to our approach. The pharmacologists (with a few distinguished exceptions) regarded us as "odd men out" and we were strangers to the psychiatrists. But there was also solid support at the core. My chief, Alastair Frazer, was a staunch friend and supported us through thick and thin. I suspect, too, that he was a little proud to have our unit emerge in a large department preoccupied with lipid transport and fat absorption. And our Dean, Professor Leonard (later Sir Leonard) Parsons, gave us, at all times, the feeling that he truly understood what we were about. Sir Leonard was succeeded as Dean by Professor Arthur (later Sir Arthur) Thomson. When, on one particular occasion, I mentioned to him the need for more clinical facilities, he readily agreed. The Queen Elizabeth Hospital built us a small research wing adjoining the Medical School. But, more significantly, the Superintendent of the Mental Hospital, J.J. O'Reilly, put at our disposal an entire clinic, which had been used to house cases of chronic schizophrenia and organic psychoses. The house had at one time been the magnificent mansion of the Cadbury chocolate family. Over a period of nine months, it was steadily emptied (a result of deliberate policy of Dr. O'Reilly's), and sometime in 1952, we moved into a beautiful, well-equipped facility – standing among old trees with a rose garden at the back – and comprising forty-four beds, a day hospital, an out-patient clinic, and even an ethology laboratory, in which Michael Chance could carry out his pioneer studies on the effect of social setting on drug activity! When we were visited by the Rockefeller Foundation and the Medical Research Council (who supported us munificently), we could present a continuum extending from laboratories to clinic, and from the Medical School to the purview of the Regional Hospital Board.

In 1951, while in the United States on a Fulbright Fellowship to study psychiatry, I received a telegram informing me that I had been appointed the Head of a newly created Department of Experimental Psychiatry in the University of Birmingham. I returned humbled, thrilled, and bewildered by this extraordinary opportunity. A dream had come true.

We did not have to wait long for another major event. Sometime in late 1952, or early 1953, there walked into my office Dr. W.R. Thrower, Medical Director of Messrs. May and Baker. Dr. Thrower told me that May and Baker had acquired the British rights for chlorpromazine and presented me with Delay and Deniker's reports (11). They had a supply and could make up the necessary tablets. Would we care to perform a blind-controlled trial? Being very impressed by Delay and Deniker's pathbreaking studies, I said we certainly would and suggested that we would do so at the Winson Green Mental Hospital. Again, I asked Charmian whether she would be interested. She was, and it was she who assumed full responsibility for the management of what was to prove, I think, a rather important step in clinical psychopharmacology. For, as I think back on it, all the difficulties, all the opportunities, all the unpredictable aspects of conducting a trial in a mental hospital were to show up clearly in that early trial: the preparation of the ward, the training of the personnel, the gullibility of us all (the so-called "halo" effect), the importance of nursing attendants, relatives, and patients themselves as informants; the use of rating scales and the calibration of such scales – all these elements came into their own, once Charmian (and to a lesser extent I) were faced with the reali-

ties of working in a “chronic” mental hospital ward. I still remember the morning when we all trooped into the boardroom of the hospital, spread the data on the large oak table, and broke the code after the ratings and side effects had been tabulated. The trial involved 27 patients chosen for gross agitation, overactivity, and psychotic behaviour: 11 were affective, 13 schizophrenic, and 3 senile. The design was blind and self-controlled, the drug and placebo being alternated three times at six-week intervals. The dose was relatively low (250 to 300 mg per day). We kept the criterion of improvement conservative, which was reflected in our discussion. Yet there was no doubt of the results: 7 patients showed marked improvement; 11 slight improvement; there was no effect in 9 patients. Side effects were observed in 10 patients. Our short paper (12), which conclusively proved the value of chlorpromazine and was the subject of an editorial in *The British Medical Journal*, was a blind self-controlled trial. But it was more, for it was a statement of the opportunities offered by a mental hospital for work of this kind, the difficulties one was likely to encounter, and the rules that one had to observe to obtain results. As we wrote (12):

The research instrument in a trial of this sort being a group of people, and its conduct being inseparable from the individual use of words, we were impressed by the necessity for a ‘blind’ and self-controlled design and independent multiple documentation. For that reason the day and night nursing staff became indispensable and valued members of the observer team. We were warmed and encouraged by the energy and care with which they did what was requested of them, provided this was clearly and simply set out at the beginning. A chronic ‘back’ ward thus became a rather interesting place to work in. There may well be a case for training senior nursing staff in elementary research method and in medical documentation. This would make for increased interest, increased attention to, and respect for detail, and the availability of a fund of information, all too often lost because it has not been asked for.

### **GROPING TOWARDS FOOTINGS OF A SCIENCE**

By the mid-fifties, the good boot of empiricism had propelled our field mightily forward. New drugs were beckoning on the horizon and facts were hunting for an explanation. Yet the *science* of it all was sparse, a mere silhouette. New methods, new facts, new connections were needed to generate new hypotheses, to fill in details, and to give the field coherence and structure.

As we were working away in Birmingham, it became apparent to me that we were dealing with a science of a very peculiar kind. It was not a discipline in a traditional sense, but an interscience par excellence. It depended on the free flow of information between disparate fields; transdisciplinary communications were situated at the heart of progress. To be sure, the component fields were developing at different rates: but they induced questions between domains which proved provocative and catalytic.

The five areas which seemed important to us at the time were *functional neuroanatomy* (as exemplified by the work of Magoun, McLean, Nauta, Jung, and Olds); neurochemistry, particularly *regional neurochemistry* of the brain; *electrophysiology* of the brain, particularly in the conscious animal; *animal behaviour* studies; *human subject studies* and the refinement of the *clinical trial*. These seemed to be footings on which the new science could stand and grow. I have expanded on these concepts in an older review (13). Nowadays, of course, we could add molecular biology and genetics.

Equally important, as one thought of it, seemed the creation of environments which would facilitate such interdisciplinary conversation. This was not always easy, but possible, as I found out in later ventures at the NIMH and at Johns Hopkins.

### INTO A WILDER FIELD: CONTACTS, MEETINGS, AND SYMPOSIA

It is hard to recapture the sheer elan and energy which developed in us all in those early fifties and the contacts which generated spontaneously as we went on in our work. The little hand-written blue airletters carried prepublication news, and were eagerly awaited. I vividly remember Hy Denber's first visit to us, soon after the publication of our chlorpromazine paper, and our discussion on dosage levels. There was an exciting correspondence with Nate Kline, whom I had first met in 1950, concerning reserpine. Later the Killams came, and a lifelong friendship ensued, and Jim Hance, who had worked for Phil Bradley and subsequently went to work with the Killams. Warren McCullough and Pitts visited us and fascinated our group with their mathematical models of self-regulation. Tinbergen (since a Nobel laureate) spoke on ethology at the Uffculme Clinic soon after it opened, and Leonard Cook, a most welcome visitor from Smith, Kline and French (SKF), shared with us some of the new and exciting techniques in the emerging field of behavioural pharmacology that he was developing. There were contacts with Ed Fellows, of SKF, who had introduced "Dexamyl," and David Rioch and Joseph Brady of the Walter Reed; later we contacted Jim Olds. Most importantly, the Macy Foundation began to organize its excellent Macy conferences on neuropharmacology, which brought us all together regularly. Also, in 1953, Hudson Hoagland organized an important interdisciplinary symposium at the Batelle Institute, at which we began, for the first time, to talk about the importance of social setting in relation to drug effects. This was called "sociopharmacology," a strange new concept to the orthodox pharmacologist. I had started to commute to the States regularly, visiting colleagues and comparing notes as the field was shaping. One such visit was of particular consequence: I believe it took place in 1952 or early 1953. A number of us met to discuss the need for an international symposium in neurochemistry, the first of its kind. Included were Seymour Kety, by that time Director of the Intramural Program for the NIMH; Heinrich Waelsch, Professor of Neurochemistry at Columbia; Jordi Folch-Pi, Director of the McLean Hospital Laboratories at Harvard; and Lou Flexner, Chairman of Anatomy at Pennsylvania. Also, I got in touch with Derek Richter and with Geoffrey Harris, who later was to emerge as a father of modern neuroendocrinology. As the theme of this symposium, we chose the "Biochemistry of the Developing Nervous System." As a place to hold it, we chose Magdalen College, Oxford. I was charged with being the Organizing Secretary, and I could not have done so without the devoted help of my British colleagues. The Symposium took place in the summer of 1954; sixty-nine colleagues from nine countries participated. It may very well be that at this Symposium the term "Neurochemistry" was used officially for the first time. As Heinrich Welch and I put it in our introduction to the Proceedings (14):

... We agreed, also, that from the start it would be well to consider the brain as a biological entity in all its complexity of morphology and function, rather than as a homogenate, or an engineering problem.

Three subsequent symposia reflected the momentum that was developing at this historic first meeting. The second on "The Metabolism of the Nervous System" was held in Aarhus, Denmark in 1956. The Proceedings were edited by D. Richter. The third on "The Chemical Pathology of the Nervous System" followed in Strasbourg, France, in 1958. The *Proceedings*

were edited by Jordi Folch-Pi. The Fourth International Symposium centered on “Regional Neurochemistry.” It was held in Varenna, Italy, in 1960. Seymour Kety and I edited the *Proceedings*.

Again, it is hard to convey the productivity that attended these meetings, as they steadily shaped some basic concepts in our field. Bit by bit, the footings of our new science were being put into place. Neurochemistry, and particularly the regional neurochemistry of the brain, was being related to electrophysiology; electrophysiology was being related to the emerging reward systems of Jim Olds, Joe Brady and Peter Dews. Behaviour analysis techniques were applied to the study of the effects of drugs on behaviour, and there was steady refinement of the clinical trial. In a word, things began to connect. In 1956, under the joint chairmanship of Jonathan Cole and Ralph Gerard, a milestone conference in psychopharmacology was held under the aegis of the National Research Council, the National Academy of Science, and the American Psychiatric Association (15), during which year also, Cole’s Psychopharmacology Service Center was created – a step of enormous consequence for the future development of the field all over the world.

In 1957, the World Health Organization invited me to convene a small study group on the subject of “Ataractic and Hallucinogenic Drugs in Psychiatry.” The following participated:

- Ludwig von Bertalanffy, USA (Systems Theory)
- U. S. von Euler, Sweden (Pharmacology)
- E. Jacobsen, Denmark (Pharmacology)
- Morton Kramer, USA (Epidemiology)
- T. A. Lambo, Nigeria (Transcultural Psychiatry)
- E. Lindemann, USA (Psychiatry)
- P. Pichot, France (Psychiatry)
- D. McK. Rioch, USA (Neurosciences)
- R. A. Sandison, England (Psychiatry)
- P. B. Schneider, Switzerland (Clinical Pharmacology)
- J. Elkes, England (Rapporteur)

I wrote the report (16), which, incidentally, carried Eric Jacobsen’s pioneer classification of the main drugs according to their pharmacological properties. In the meantime, the scientific command of the U. S. Air Force, through its principal representative in Europe, Colonel James Henry, had catalyzed meetings, at which the international implications of brain research became steadily more apparent. After preliminary meetings in 1958 and 1959, a number of us met at UNESCO House in 1960 to draft the Statutes and Bylaws of IBRO – the International Brain Research Organization. The disciplines of neuroanatomy, neurochemistry, neuroendocrinology, neuropharmacology, neurophysiology, behavioural sciences, neurocommunication, and biophysics were represented. Dr. Daniel Bovet and I represented Neuropharmacology in the first Central Council of IBRO. Our emerging field had now a major international presence.

### TOWARDS THE CINP, THE ROME CONGRESS, THE NIMH, AND HOPKINS

In te Spring of 1955 or 1956 – I cannot remember which – Professor Ernst Rothlin and Mrs. Rothlin paid us a leisurely three-day visit in Birmingham. During our conversations, in which Charmian, Philip Bradley, William Mayer-Gross, and I participated, two broad ideas kept surfacing. One was the need for an international forum to discuss and serve the advances in our field. The other, the need for an international journal. I do not rightly recall whether the Latin name of *Collegium* was used in our discussion, but the need for an organization certainly kept recurring.

As for the journal, preliminary work had already been done. Willie Mayer-Gross had been in touch with R. Jung of Munich. Springer, the publishers had been approached and appeared interested. Further discussions involved Jean Delay, P. Deniker, P. Pichot of Paris, and most importantly, Abe Wikler of Lexington. It took quite a number of telephone calls and letters to persuade Abe to assume the co-editorship of this new journal. I served on the editorial board and still recall the excitement when the first slim yellow issue of *Psychopharmacologia* landed on my desk.

Perhaps this is also the place to emphasize the prescient vision of psychopharmacology that Abe Wikler had developed at the time. He saw, long before most of us, the true dimensions of the field, defining it beautifully in his book on the *Relation of Psychiatry to Pharmacology*, (17) now out of print. It set a standard of rigour and excellence – a standard he set for *Psychopharmacologia*, which continued as a model for years to come. Our contacts with the Rothlins and the Sandoz Group remained very much alive.

In 1957, at the invitation of Seymour Kety and Robert Cohen, I moved to the United States to establish the Clinical Neuropharmacology Research Center at St. Elizabeth Hospital, where Nino Salmoiraghi, Steve Szara, Hans Weil-Malherbe, Fritz Freyhan, and Floyd Bloom, joined us in rapid succession. Max Hamilton was our first visiting scholar. After I left (in 1963), Nino Salmoiraghi assumed the directorship. He was followed by Floyd Bloom and later by Richard Wyatt, the present incumbent.

Philip Bradley remained in contact with European colleagues. As he, Deniker, and Radouco-Thomas reported (17): At a meeting on psychotropic drugs in 1957 in Milan, “a small group of interested people representing pharmacology, psychiatry, psychology, and so on, held informal discussions and decided that regular opportunities should be provided for workers in the various fields of research and clinical investigation, to meet and discuss their common problems.” The idea was taken further at the Second International Psychiatric Congress in Zurich in September of the same year (I could not attend, having just moved to Washington). It was at this Congress that our new *Collegium* was formally inaugurated, and it was Professor Trabucchi’s invitation which led to our first Congress in Rome in 1958.

I attended the Congress, co-chairing the third Symposium and reading a paper on the “Relation of Drug Induced Mental Changes to Schizophrenia” (18) at the fourth. Across a span of nearly fifty years, one cannot help but be encouraged and thrilled by the vision of the organizers and the sheer span, grasp and inclusiveness of the program. For at what earlier international forum had the four footings of our science – neurochemistry, electrophysiology, animal behaviour, and the refinement of the clinical trial – been so skillfully juxtaposed? Where had one encountered papers on the measurement of subtleties of subjective experience in drug-induced states and discussed rating scales for subjective experience and objective behaviour?

Or had been considered, in context, the huge policy implications of the psychoactive drugs for the mentally ill? I feel that by the end of the Congress, the silhouette had filled out and sharpened, presenting a new landscape in clear light. Biochemistry, physiology, psychology, and behaviour were looking each other in the face in a new kind of recognition. We had a map. It is exciting to recall this historic encounter.

As for my own paper (19), I could only submit an abstract – having been preoccupied with our newly-formed group in Washington. I presented an expanded version of the same ideas at the Third International Neurochemical Symposium in Strasbourg during the same year. In this paper (20), I examined schizophrenia as a possible disorder of information processing by the brain, drew attention to the possible place of subcortical structures (putamen, caudate, globus pallidus, and hippocampus) in the processing and misprocessing of such information, and considered the role of amines, particularly serotonin, norepinephrine, and dopamine in such misprocessing.

In 1963, I was invited to assume the chair at Johns Hopkins and the directorship of the Henry Phipps Psychiatric Clinic. But this “epistle” is already far too long, and I must defer details of this most fruitful and meaningful period to another occasion. Let me simply say that, at Hopkins we went on doing “more of the same.” Sol Snyder began his pathbreaking neurochemical studies while still a resident, and now heads up the superb Department of Neuroscience at Hopkins. Joe Brady built primate laboratories for his far-reaching program in behavioural biology. Joe Coyle advanced developmental neurobiology in a way which inspired many residents to follow in his footsteps; he is now chief of Psychiatry at Harvard. Ross Baldessarini is director of the Mailman Laboratories at Harvard. “Uhli” Uhlenhuth, Lino Covi and Len Derogatis developed their rating scales and engaged in important outpatient studies. Uhli was also president of the ACNP at its twenty-fifth anniversary. Last but not least, reaching back to joint times at the NIMH, Floyd Bloom is now editor-in-chief of *Science*. There are many, many others one wishes to mention, but ‘tis time to stop.

## CLOSING

In 1961 the newly constituted American College of Neuropsychopharmacology did me the immense honour of electing me as their first president. Looking back on my year of service, I said (21):

It is not uncommon for any one of us to be told that Psychopharmacology is not a science, and that it would do well to emulate the precision of older and more established disciplines. Such statements betray a lack of understanding for the special demands made by Psychopharmacology upon the fields which compound it. For my own part, I draw comfort and firm conviction from the history of our subject and the history of our group. For I know of no other branch of science which, like a good plough on a spring day, has tilled as many areas in Neurobiology. To have, in a mere decade, questioned the concepts of synaptic transmission in the central nervous system; to have emphasized compartmentalization and regionalization of chemical process in the unit cell and in the brain; to have given us tools for the study of chemical basis of learning and temporary connection formation; to have resuscitated that oldest of old remedies, the placebo response, for careful scrutiny; to have provided potential methods for the study of language in relation to the functional state of the brain; and to have encouraged the Biochemist, Physiologist, Psychologist, Clinician, Mathematician, and Communication Engineer to join forces at bench level, is no mean achievement for a young science. That a chemical text should carry the imprint of experience, and partake in its

growth, in no way invalidates the study of symbols, and the rules among symbols, which keep us going, changing, evolving, and human. Thus, though moving cautiously, Psychopharmacology is still protesting; yet, in so doing, it is, for the first time, compelling the physical and chemical sciences to look behaviour in the face, and thus enriching both these sciences and behaviour. If there be discomfiture in this encounter, it is hardly surprising; for it is in this discomfiture that there may well lie the germ of a new science.

In our branch of science, it would seem we are as attracted to soma as to symbol; we are as interested in overt behaviour as we are aware of the subtleties of subjective experience. There is no conflict here between understanding the way things are and the way people are, between the pursuit of science and the giving of service. So we must go on along lines we began: talk to each other, and keep talking. Psychopharmacology could prove a template for a truly comprehensive psychiatry of the future. We must train colleagues who do good science and, above all, who also *listen*: For, like it or not, our humanity will never leave us in our molecular search.

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## 4 INTERVIEWS

Joel Elkes was interviewed twice for An Oral History o Neuropsychopharmacology. Both interviews were conducted by Fridolin Sulser.

The first interview was conducted on December 12, 1995 at the annual meeting of ACNP in San Juan, Puerto Rico. The transcript of this interview is included in Volume One (Starting Up) of the series.

The second interview was conducted on October 14, 2008 at the Fetzer Institute in Kalamazoo, Michigan. The transcript of this interview is included in Volume 10 (History of the ACNP) of the series.

#### 4.1 FIRST INTERVIEW

Interviewer: Fridolin Sulser

Site: San Juan, Puerto Rico

Date: December 12, 1995

FS: Joel,\* welcome to ACNP History Task Force. It is quite a thrill for me to interview you as the first President of the ACNP. Now, the task force, the History Task Force, has imposed some rules, which we can follow, or if we like, we would not follow. So, one of the first questions they want me to ask you, is about your early educational experiences and the determining factors in your entering medical school.

JE: Well, as you probably know, I was raised in Lithuania and I went to secondary school in Lithuania; my father was a very prominent physician there. So I had the paternal example of my father, who had, himself, been educated in Koenigsberg, now Kaliningrad, Russia, across the border in Germany, and had a really deep regard for both the practice of medicine, in which he was superb, and the science of medicine. I had always engaged, at least in my early days, towards the middle of my school years, in a dialogue between physics and medicine. I was deeply interested in physics. I spent my first prize monies on works describing the new physics and still remember the awe with which I'd viewed of collision paths of particles in a cloud chamber. I really wanted to go into physics, but I didn't have the mathematical equipment for that. I was kind of shy of mathematics. But then, at the same time, in discussing things with my father and friends, there was much talk about the sciences compounding medicine, physiology, of course. But the term biochemistry was still an unknown. The sheer concept of biochemistry – a chemistry of life no less – was still a strange concept. So, we talked about chemistry and life and life processes, and I remember discussing this and thinking to myself, well, maybe I can sort of ride into medicine by way of chemistry and physics, and get an idea of the sciences serving medicine and still keep my beloved physics with me. Then the main decision point came, and because I had such a superior example of physicianship in my father, I decided to go into medicine – by way of physical chemistry, organic chemistry, and surface and colloid chemistry. At all times I was pulled by

physics, and this continued for quite some time, after I entered medical school. So, the answer is, I went to medicine because I had a secure example of good physicianship and a good person, in my father, and because I also hoped that medicine would lead me to a sort of relationship of science to life and nature. So I was becoming a physician, and also becoming a scientist serving medicine.

FS: What I was wondering about how you then, after you finished medical school in London, chose psychopharmacology. This was in its infancy at that time. Maybe that was the reason for your choice?

JE: Well, that is a complicated question, again, because very little was known about the effects of drugs on the mind, and I was a student at St. Mary's Hospital, London, at the time. Quite honestly, I didn't see that as a tremendous interest, then. But while a student I became interested in immunology: There was a giant in the field at St. Mary's. He influenced me.

FS: Immunology?

JE: There was Sir Almroth Wright, the father of the typhus vaccine, who was a model for George Bernard Shaw in the "Doctor's Dilemma". There was also my Dean, Sir Charles Wilson, who later became Churchill's physician. But "psychiatry" was a tiny, tiny fragment of the curriculum taught in far too few lectures and demonstrations. This excited me tremendously. I went after psychiatry and read avidly, and began to try to connect, in my confused mind, physical chemistry, immunology, and mental function. How do chemistry of the body and brain relate to each other, how does it connect with mental function? The drugs, which were then existent, were very, very ordinary drugs. But we did not precisely know how they worked.

FS: Joel, let me interrupt you. I always felt that your three heroes, whom you mentioned in your ACNP lecture, had something to do with this. You mentioned Einstein and physics; you mentioned Goethe; and, then, you mentioned Ehrlich and his receptors. Now, most people will understand why Einstein; they will understand why Ehrlich; but Americans do not know Goethe. Why Goethe? I know why, but I think Americans should know why.

JE: Well, Goethe was, to me, an extraordinary example what a human being – a person – can achieve on this planet. He was a poet – a master of both prose and poetry; he was Minister of State for the Duke whom he served; a theater director; and, as a hobby, almost, a scientist. Goethe

studied the origin of plants; he studied light and the theory of colors. This rare combination of humanism and scientific creativity and the spirit filled me with immense admiration. It's just as simple as that. He was an example.

FS: So if my assumption is correct, that had something to do with you trying to get into pharmacology, combining chemistry, physics, and psychiatry at the same time?

JE: Oh, yes, whatever psychiatry was at the time I read avidly. Freud, of course, his view that the future would produce physical markers for mental events, impressed me – something like that – I'm paraphrasing. But the drugs didn't really come into view until right after medical school, by which time in 1941, I went to Birmingham, England to follow my friend, Alastair Frazer to the Department of Pharmacology. This Department was an extraordinary department because from an early modest beginning, Frazer and myself, it grew to a large, significant, influential department, and had a very strong grounding throughout. Why? It happened because Frazer was a self-taught and self-sufficient physiologist. He was interested in fat absorption and the physics of the chylomicrons, tiny particles that flood the blood after a fatty meal. I became interested in the protein/lipoprotein covering of these particles, which stabilized this natural emulsion in the blood stream. When I started to work on lipoproteins, it was known that lipoproteins were built into the architecture of membranes – and I started to think about the stability of the membrane surrounding the chylomicron and thus found myself back in physical chemistry. This work proceeded during the War. We learned of very specific molecules – the nerve gases, the anticholinesterases – which had a high affinity for the nervous system.

FS: That was your entry to the brain?

JE: That was one entry to the brain. On the other hand, I'd already worked in physical chemistry and the structure of biological membranes – lipoproteins. Suddenly I realized that the nervous system was full of lipoproteins. It was myelin, a beautiful paracrystalline structure ubiquitously distributed in the nervous system. I was fortunate, as my first PhD student, Bryan Finean, was a crystallographer who undertook the arduous task of studying the X-ray diffraction structure of living myelin. We decided to plunge into that field, the structure of a naturally occurring lipoprotein, which probably held special bioelectrical properties in the nervous system. Francis Schmitt had studied dried myelin, his classical work was a guide to studying living myelin

became a challenge. Finean and I constructed a special chamber for irrigating a living sciatic nerve preparation which made it possible to shoot X-ray beams through a living structure while the environment of a segment of nerve was being changed systematically. We studied the effect of gradual drying, irrigation with alcohol and ether on the crystal structure. The changes were orderly, repeatable, and to some extent reversible. The X-ray diffractive diagrams were clear and quite, quite beautiful. To this day, I cannot really tell you what possessed me to do this. I suppose it was the vain hope of seeing the penetration of molecules of an anesthetic into the molecular structure of myelin. However, suddenly I was in the nervous system! I hoped it could lead to visualizing the effects of drugs. At that time there was no real neurochemistry. There was Quastel's great work on the effect of barbiturates on glucose metabolism in brain homogenates. There was Richter working on cognate problems. My dream of specific attraction to certain receptors had to wait. We began to map the cholinesterases in certain parts of the brain. It was an indirect, confusing, and confounding journey. But I was into the brain. I was also an outsider, reading wildly, edging towards a neuropharmacology of behavior. There were very few people I could talk to at that time. I chose the anticholinesterases and the role of acetylcholine. I also read Sherrington. Also, as it happened, I saw for the first time, sitting safely in the back of the auditorium, a demonstration at the Physiological Society in Cambridge by Lord Adrian, the great Adrian. He touched a vibrissa of a cat. There was a loud 'humph' on the loudspeaker. He touched another. There was silence and I sat there in the back, totally awed by the precision of the phenomenon, and I went up to Lord Adrian, at the time, and told him of my interest. He said, "well, you're not really in physiology – you are in pharmacology." And I said that I really felt that pharmacology could lead us to physiology, understanding of the way the brain does it naturally without the aid of chemical prostheses: This gradually became a main theme in my thinking: pharmacology as an approach to physiology. We started working on the cholinesterases and their regional distribution. At that time, acetylcholine was the main molecule in the central nervous system. This was due to Sir Henry Dale's influence.

FS: Joel, this is still a long way to psychiatry, but it didn't take very long. It was in 1951, a milestone in your career, when you established the Department of Experimental Psychiatry in Birmingham, which is said to be the first of its' kind in the world. Tell us a little bit about it.

JE: Well, before I do, I must refer you to several developments which took place before 1951. The first was that my late beloved wife Charmian and I started to work, for the first time in my career, in a mental hospital setting. I became very interested in the effect of drugs on the brain from my wide reading. About that time, we were in London, and heard of the effects of drugs on catatonic (schizophrenic) stupor from some French colleagues.

FS: Was this about 1948 or '49?

JE: About 1949. We started to look around for the syndrome in our own hospital and identified some 22 cases. We began to study the effects of Amytal (amobarbital), amphetamine, and mephenesin on the syndrome. We studied effects on mental function, on speech, and on other psychological response, and also on blood pressure and foot temperature. These catatonics had a very striking syndrome. They were characterized by slate blue legs, arms, hands, and were non-verbal, not giving any indication of being present and aware. Given Amytal in doses that would put you or me to sleep, 350 or 400 milligrams, they came out of the stupor. This effect was very dramatic: they would talk; they would draw; they would write and they would communicate; and then, like in an Andersen fairy tale, they would relapse into a deep sleep. We'd measure foot temperature and would find that there was correlation between vasodilation, foot temperature, and psychomotor response. The process lasted for about three-fourths of an hour. Giving amphetamine in doses which would send you or me into wild excitement, these people deepened their stupor, and at the same time, there was sharp vasoconstriction and a sharp rise in blood pressure. We also had mephenesin, which had just been introduced as a muscle relaxant by Frank Berger; the catatonic rigidity was strikingly reduced but there was no psychomotor response. In other words, there was specificity in the drug response effects, and we wondered whether what we were dealing with was a state of hyperarousal. This was one piece of work which established us in the mental hospital culture; however, there was nothing between the patient and the laboratory, we needed another intermediate point. The effect of drugs on the electric activity of the brain and the conscious animal suggested itself quite early; but no technique to do this was available. It is at this point that Philip Bradley entered my life as my second PhD. student. Philip had had a background in zoology in the University of Bristol. He had worked on insects. We wondered whether a technique for implanting and recording in the unanaesthetized animal was feasible. Philip said "yes," and for two years worked on developing techniques for recording electrical activity in the

conscious and unrestrained animal. Bradley's cats became quite famous. They lived happily in the lab for up to nine months. No infection: I might say that the implantation occurred before the advent of penicillin. Prophylactic use of sulfonamides was the rule. The results were very striking. We began with the anticholinesterases, acetylcholine blockers and amphetamine. We studied cortical and sub-cortical activity and looked for correspondence between electrical activity and behavior. We found that with cholinergic and anticholinergic drugs there was no correspondence between electrical activity and behavior. With amphetamine there was such correspondence, and the effects depended on intact connections to the mid-brain. This brought to mind Moruzzi and Magoun's work on the waking brain. At the same time, Marthe Vogt presented her findings on the presence of norepinephrine in the areas of the brain implicated by our experiments. Yet it was so tedious to do this work at this time. You dissect areas of the brain, you homogenize the various regions, and then you incubate the eluate in the Warburg nanometer. You test the eluate against a guinea pig ileum for potency.

FS: This is interesting, Joel. This is somewhat parallel to the studies that my teacher, Walter Rudolph Hess, did in Zurich. You know, if I remember correctly, he worked on the conscious cat in 1950. So it is quite parallel.

JE: Yes, and Geoffrey Harris, my colleague at St. Mary's Hospital and later a founding father of neuroendocrinology, visited Dr. Hess at the time. We ourselves had no contact with Dr. Hess. In any event, the results were very striking. We wondered what we should name our little unit. They wanted to call it Chemical Psychiatry, and I said, "No" and stuck with the term Experimental Psychiatry because I really believed that the experimental method is necessary to make psychiatry a science. In 1951, the University graciously named me head of a small department with that name. The department comprised: neurochemistry, represented by our work on the anticholinesterases; there was also electrophysiology, represented by Bradley's and my own work on conscious cats; there was animal behavior; and later ethology, represented by Dr. Michael Chance, a member of our department; and there were the clinical studies in catatonic (schizophrenic) stupor. We thought we had the footings of the field in place.

FS: Joel, another milestone that happened there was the first controlled trial with chlorpromazine. Could you elaborate on that?

JE: Again, I can only recall the occasion. We had just founded our Department of Experimental Psychiatry and we had a research facility at the Winton Green Mental Hospital. About this time there came to my office, Dr. W. R. Thrower, clinical director of Menley and James, a big pharmaceutical company. He said this was not a routine visit. He was very formal and unlocked his briefcase, and out of it came a paper in French, which was the account of the action of a hitherto unknown compound, an antihistaminic, on the behavior of schizophrenic patients. I read it with slight disbelief, and said I would like to know more about it. Dr. Thrower said that's why he came; Menley and James had acquired the rights for the substance and had a supply of it in their safe. They could make up tablets and placebos for a trial. Would we carry on a controlled trial? I went to Charmian, again, and said "here is something"; I did not know the magnitude of it, "should we do a trial?" In her characteristic way, she said, "yes," because by that time she had established a base in the mental hospital. She quickly accepted the full responsibility for the trial. We had colleagues whom we could interest in the project; but it was she who designed the trial, as a blind self-controlled design, and selected the patients. 27 patients were involved with about 13 schizophrenics, some with affective disorders or organic syndromes. Overactive behavior was the main criterion for selection – the trial lasted about 22 weeks. And one day, one Saturday morning, we trooped down into the boardroom of the mental hospital, and spread the data on a big oak table. The code was broken and the record emerged. No statistics were necessary in seven patients. These patients had benefited strikingly and relapsed on placebo. The trial noted side effects and weight gain, effects that were at the same time described by others. However, most importantly, we learned much from the conduct of the trial itself. Allow me to read from the copy: "Perhaps we may be allowed to draw attention to one last point – namely, the lessons we feel we have learnt from the trial itself. The research instrument in a trial of this sort being a group of people, and its conduct being inseparable from the individual use of words, we were impressed by the necessity for a 'blind' and self-controlled design, and independent multiple documentation. Furthermore, we were equally impressed by the false picture apt to be conveyed if undue reliance was placed on interview alone, as conducted in the clinic room. The patients' behavior in the ward was apt to be very different. For that reason the day and night nursing staff became indispensable and valued members of the observers' team. We were warmed and encouraged by the energy and care with which they did what was requested of them, provided this was clearly and simply set out at the beginning. A chronic 'back' ward thus became rather interesting place to work in. There may well



be a case for training senior nursing staff in elementary research method and in medical documentation. This would make for increased interest, increased attention to, and respect for, detail, and the availability of a fund of information, all too often lost because it has not been asked for.”

FS: You know, someone with your mind must have had some very profound thoughts about chlorpromazine. It was long before we knew about dopamine D-2, D-1, D-4 or what have you, how a drug could affect behavior. I find it incredible; this is one of the milestones in psychopharmacology. Tell us the impact it has had on the evolution of the entire field.

JE: Yes, let me track back a little, because by that time I had slowly developed the view that we were dealing with indirect effects of the drugs on families of naturally occurring substances.

FS: Yes, this is interesting. Let me tell you something quickly that might interest you. When I came to the United States with a suitcase in October 1958 and walked in to Brodie’s laboratory, there was Arvid Carlsson showing the uneven distribution of dopamine in the brain, showing an enormous concentration of dopamine in the striatal areas. From the uneven distribution of dopamine he got to the conclusion that dopamine is more than a precursor to norepinephrine. I think this was in keeping with your thinking.

JE: Yes, yes, we began to talk about regional neurochemistry. Seymour thought about regional differences in cerebral circulation and I thought about regional differences of neurotransmitters and families of naturally occurring compounds that had arisen in evolution to modulate and guide the interaction of neurons, and regulate excitation and inhibition in the nervous system – I thought of regional field effects in the nervous system.

FS: At a UCLA symposium.....

JE: At UCLA, yes. The concept of regional chemistry was getting through. By that time we began to think of “how do we create a conversation on the subject?” This is how the idea of these symposia on regional neurochemistry arose. I believe it was, 1954 or ’56; Seymour Kety, Heinrich Waelsch, Jordi Foch-Pi, Louis Flexner represented the United States, and Geoffrey Harris and Richter, and myself, the United Kingdom.

FS: I was wondering if you could make a few comments on using the drug as a tool to unravel mechanisms. I mean, it's obviously something you were thinking about.

JE: Very much so. With the cholinesterases, it's important because cholinesterase and anti-cholinesterase has opened up the whole area of acetylcholine synthesis and its role in normal functions. So, to come back, to a general statement, I really feel that pharmacology, as we know it, will lead us to a deeper understanding of the body's natural inner pharmacy. It may give us a footing for a natural healing system.

FS: Joel, I couldn't agree more with you. I think that using these drugs wisely as tools has contributed more than anything else to the dissection of mechanisms. Listen, this is wonderful. Now, comes the big jump, and I don't quite understand why you made this big jump over the ocean to Washington, D.C. in 1957. You were in England and all of your friends were there. You had your former wife there and everything was working fine.

JE: Everything was working wonderfully.

FS: Why did you come to St. Elizabeths?

JE: First it came from a deep personal relationship with Seymour Kety, Bob Cohen, and Bob Felix and their openness to ideas. I found it extremely hard to leave England. The University, the Medical Research Council, the Rockefeller Foundation could not have been more generous and rewarding; the field was developing very fast in the United States, and I wanted to be part of it. When we started, our department started getting visitors every week. Wonderful conferences at which the idea of families of naturally occurring compounds were expressed. As far as I remember, I first expressed it in an invited paper to the newly founded Mental Health Research Fund in 1952 and developed it further in our paper in 1957: Let me quote again: "Perhaps rather than thinking in unitary terms, it may at this stage, be advisable to think in terms of the possible selection by chemical evolution of small families of closely related compounds, which by mutual interplay would govern the phenomena of excitation and inhibition in the central nervous system. Acetylcholine, nor-adrenaline and 5-hydroxytryptamine may be parent molecules of this kind; but one has only to compare the effects of acetylcholine and succinylcholine, or nor-adrenaline with its methylated congener to realize how profound the effects of even slight changes of molecular configuration can be. The astonishing use which chemical evolution has made of the steroids is

but another example of the same economy. It is likely that neurons possessing slight but definite differences in enzyme constitution may be differentially susceptible to neurohumoral agents. Such neurons may be unevenly distributed in topography close, or widely separated areas in the central nervous system, these differences probably extending to the finest level of histological organisation. Phylogenetically older parts, and perhaps, more particularly, the mid-line regions and the periventricular nuclei may, in terms of cell population and chemical constitution be significantly different from parts characteristic of late development.”

I cannot describe to you the intensity with which I saw, in my mind’s eye, these naturally occurring molecules distributed regionally in the brain. When, much later, I saw the Swedish fluorescent photographic evidence, confirming their uneven distribution, I experienced a shocked feeling of awe. The idea of a regional neurochemistry took root. In those years I had, peripherally, become active in neurochemistry. I was organizing secretary of the first international neurochemical symposium, which took place at Magdalen College, Oxford in 1954. Other symposia followed, the third being held in Ravenna, Italy, convened by Seymour Kety and myself on the theme of ‘Regional Neurochemistry’.

FS: Now I come to your center at St. Elizabeths. So it was actually you who catalyzed the development of that center, the organization?

JE: Well, there was nothing there.

FS: There was nothing there?

JE: Nothing, nothing there at all.

FS: It was just walls.

JE: It was just the William A. White building, a 300 bed chronic hospital.

FS: It was like an old chronic hospital.

JE: Yes, we came in with a budget to Dr. Shannon with Bob Felix, Bob Cohen, and Seymour Kety, and we put out the labs in the basement, and the administration at the top between patients who were all around us. That was the beginning of what became the Clinical Neuropharmacology Research Center. I was the first director of that center. In fact, to tell you, I remember that, there

was helluva timetable getting it done. As a matter of fact, Seymour sent me the floor plan of the basement of St. Elizabeths to England, the catalogues, and said, "please design labs, because we need it now". I designed the labs in Birmingham, England. And then, we came to present it to the director of NIH, Dr. Shannon, one Sunday morning and he approved it readily, actually increased our budget. I could tell you a good story about that one.

FS: So, this is how.

JE: And then we recruited the various people. One of my first recruits was Hans Weil Malherbe.

FS: This is another thing that I think is very, very significant. You have always been able to recruit superb people.

JE: Well, I brought Weil Malherbe from England. He started his own lab. He was very early in, in the amine story and he started to collaborate with Julie Axelrod.

FS: It was about the time when I came to Brodie's lab.

JE: And then we had Fellows, many, many, too numerous to name.

FS: And Max Hamilton.

JE: And Max Hamilton spent a time with us and wrote, in fact, his famous Lectures on Methodology while he was a Fellow at St. Elizabeths.

FS: And, Paul Bender was there.

JE: Oh, yes. I can't remember all the names.

FS: Joel, what do you consider as the major accomplishment in your unit? You were there from '57 till '63?

JE: Till '63.

FS: This is a tough question to ask.

JE: At the fundamental level there were really three accomplishments.. There was Floyd Bloom's work with Nino Salmoiraghi on the electrophysiological response of individual neurons to different transmitters, providing chemical evidence of inhomogeneity at the unit level. And then, there was Weil Malherbe work on the amines, which then linked up with Julie's work.

FS: You're right, yes.

JE: Then there was work on the effect of metabolites on animal behavior, which Steve Szàra did. He showed that tryptamine derivatives had a differential effect on conditioned behavior. There was Fritz Freyhan's fine work on the whole concept of what he referred to as Comprehensive Psychiatry, which included drug effects, but also emphasized the active social support system and the analysis of the factors which played the part in the recovery of the individual patient. Mainly, a culture was created and conversation proceeded. It was a wonderful, heady, exciting time in the middle of a very chronic mental hospital. There were people coming virtually from all over the world and there were talks and discussions and excitement. At the same time, there was also always and always, which is what we had hoped, the presence of the patient. For example, you go to the canteen for lunch and there's a schizophrenic hallucinating under a tree. You're never very far away from the problem that brought you here. And, gradually there developed a sense of place, a sense of belonging. Gradually, I realized that, my God, together we created something pretty wonderful.

FS: You know, Joel, what impresses me about this whole thing is that you never imposed yourself on these people and you've never put your name on the papers. You supported them. You discussed the importance of their work, but you did not impose your name on papers like Floyd Bloom's. It's amazing, you know. You were a gentleman.

JE: One is a chief. One is a good gardener. The institute is a sort of greenhouse, one who identifies plants, grows, and one makes sure that people have everything that they need. I'll give you an example that comes to mind. There was Richard Michael. Richard Michael, a very good neuroendocrinologist, is now in Atlanta, Georgia, but at that time he was a pupil of Geoffrey Harris. He needed radioactive estradiol to implant into the hypothalamus to show the effect of hormones on sexual behavior, which was very specific in terms of both the hormone and the location of the hormone and the uptake of the hormone in certain cells of the hypothalamus. He

gave me one hell of a time trying to find this damn radioactive estradiol but we did. We got the stuff. When he published his paper, it was really quite a remarkable paper he showed the distinct contribution of certain cells of the hypothalamus to sexual behavior. My job was to cultivate talent. I did it in Birmingham. I did it at St. Elizabeths and the Research Center, and then I hope I did it again at Hopkins.

FS: Joel, I think this is a matter of style, and this was the Joel Elkes' style, helpful and wonderful style. That leads me to the next step in your career. In 1963, you went to Hopkins and it was there where you actually would have got a stellar group of pre-clinical and clinical neuroscientists put together. This is quite unique, you know.

JE: Well, again, I was just so fortunate. For one thing, I was awed to step into the shoes of the ones who preceded me, Adolf Meyer, Whitehorn, and Seymour Kety. When I started, my office was next to Adolf Meyer's library, and I started reading his convoluted English and his more convoluted German, but, my God, what clear concepts the man had. He struggled with the term psychobiology for years. His Salmon lectures were significantly published after his death. I felt that sounded right to me: Psychobiology – biology of mental life – was a good fit between me and the job. There was also a fit between my temperament and the total climate. This was not a shiny new institute. It was an old, old brick building, with old smells, and had animal laboratories in the building. On the third floor, there was Curt Richter who did all his magnificent work on chronobiology in rats. So there was a wonderful tradition. There were also some great people around already, Horsley Gantt, the only surviving pupil of Pavlov; Jerry Frank, the author of *Persuasion and Healing*; John Money, one of the best authorities on sexual behavior in man, and more and more junior colleagues. These substantial figures were ranging from biology to psychoanalysis. The comprehensiveness was congenial to my view of psychiatry, and I wanted to convey the comprehensiveness to medical students to give them templates on which they could build. I reflected that view in the way. I named the department, Department: Psychiatry and the Behavioral Sciences; I intended to start students off with a course in Basic Behavioral Sciences. However, there was no time in the curriculum for behavioral science. So we organized a course on Saturdays. Four strands formed the core; Human Development, Human Learning, Human Communication and the Social Field. The course was shot through with biology at every stage. The other thing, which we did, was to recruit the Chairmen of the other departments, to teach in

our introductory course: Alan Barnes, Chief of Gynecology and Obstetrics, Robert Cooke, who was Chief of Pediatrics, colleagues from Harvey's Department of Medicine, and Blalock's Department of Surgery gave introductory lectures in our course which was really an introduction to medicine as a whole. Suddenly, psychiatry became alive and connected to other departments. I gave the introductory lectures myself; the response was encouraging. The students noted the change and responded magnificently. Residents suddenly shot up. There was a tremendous competition for the few residents' posts that we had. Wonderful people appeared. Sol Snyder, Joe Coyle, and Ross Baldessarini were residents at Hopkins.

FS: You obviously transferred your enthusiasm and your views to these people. I think this is one of your major contributions: nurture of people, your support of people.

JE: Yes, but, you know, that brings me back to my youth again, and my parents. They were extraordinary, nurturing people. They made me feel wanted and secure, and at the same time, there was always, always, the questioning spirit, the wish, to understand, the 'why'? That's what really ensued; somehow, invariably everywhere in Birmingham at St. Elizabeths and Hopkins. There were some fine, fine conversations in my youth.

FS: Joel, I have you rushing a little bit, but I have to come to questions that the ACNP wants me to ask you for 'history'. If you look back on fifty years, in psychopharmacology, who were the scientists who had the most impact on your work, who would you single out?

JE: This is a hard question. Sherrington, one of the giants in early neuroscience, is one; Lord Adrian, who had tremendous depth, and inordinate experimental skills, is another.

FS: Was there anybody in the clinical area?

JE: In the clinical area, Adolf Meyer, because of the comprehensiveness of his approach. I'm hard pressed to answer this question, because there were so many, but among my contemporaries.....

FS: Seymour Kety, obviously?

JE: Seymour represented again, a wonderful blend of comprehensiveness, precision, and humanity. You know, I've known scientists, great scientists. They impressed me by their ideas,

but when I'd got to know them often they were a little disappointing. Seymour had a tremendous influence on me as a person. He was gentle, he was human, he thought clearly, and had a contagious Woody Allen sense of humor. Then there was Heinrich, Heinrich Waelsch, the Dean of neurochemistry at that time; he had a continental acerbic sense of humor, a delight. He had a tremendous style.....

FS: He was at Columbia.

JE: He was at Columbia. He did all of the work on ammonia and the brain. Heinrich Waelsch, Seymour Kety, Jordi Folch, and myself with Geoffrey Harris and Derek Richter convened the first Neurochemical Symposium at Oxford in 1954. We really convened the leaders of neurochemistry when it was first beginning. Nino Salmoiraghi and Floyd Bloom came into my life late – absolutely wonderful workers. Floyd was always seeing the big picture. His brilliance and his imagination were always showing. Ross Baldessarini, as resident, was showing a balance between being a gifted psychotherapist when he was a resident, and a damn good biochemist in the lab. And I could go on and on, but to answer your question, the giants in my life mentioned above influenced my life by the way they thought more than anything else.

FS: Now, you have to put your modesty aside for the next question. The ACNP asked me to ask you what do you think, Joel, were your greatest contributions to the field?

JE: At the conceptual level, very early, the concept of families of neuroregulatory compounds, their uneven distribution in the central nervous system and the key role in this concept of regional neurochemistry played in understanding the mode of action of psychoactive drugs, and in understanding how the brain does it without drugs. Secondly, the role of pharmacology as a gateway to physiology, to understanding how the brain works naturally, without the chemical prostheses of drugs – pharmacology as a way of exploring the phenomena, the layering, the organization of mental life, and giving us an insight into schizophrenia as a disorder of information processing in the brain.

FS: We, today, start talking again about the cross talk in the brain, you know.

JE: Yes, it's in that paper that Bradley and I wrote that we talk about it. And, in the CIBA symposium paper, I'm quite specific about the interaction between drugs and families of naturally



occurring compounds. Another contribution was the importance of understanding the interaction between environment – the social setting – and the action and, even, the dose of a drug; the same drug in the same person in the same dose can produce different effects according to changes in the environment which precede, or accompany, or follow the administration of the medication. Thirdly providing a setting where intelligent conversation between neurochemistry, electrophysiology, and behavior, and subjective experience could take place – and where experiment interacts with clinical experience. This was the Department of Experimental Psychiatry. I tried to be a good gardener and cultivate transdisciplinary.

## 4.2 SECOND INTERVIEW

Interviewer: Fridolin Sulser

Site: Fetzer Institute, Kalamazoo, Michigan

Date: October 14, 2008

FS: It is Tuesday October 14, 2008. We are in the main boardroom of the Fetzer Institute in Kalamazoo, Michigan. I am Fridolin Sulser and I have the great honor and privilege to interview, Joel Elkes for the fiftieth celebration of the ACNP in 2011. Joel has been the first president of the ACNP. He has been there at the inception of the college and he played a key role in the evolution of the two interrelated fields, basic neuropsychopharmacology and biological psychiatry. He made his mark with his visionary approach of linking basic research and clinical psychiatry. I'd like to start the interview, Joel, by asking you a few questions about your background and how you got involved with neuropsychopharmacology before we talk about the inception of the ACNP in 1961. You could start telling us a little bit about your background; where you came from, your education and your involvement with the field.

JE: Well Fridolin, it is a very special honor for me to talk to you about something which happened fifty years ago or longer. I, as you know, was born in Koenigsberg, in Eastern Prussia on the border of Lithuania, a Baltic Country on the border of Russia in the seat of the Knights of the Junkens of Germany. I went to a school in Lithuania, where every subject, from trigonometry to Voltaire, was taught in modern-Hebrew. Teachers were masters of their subject, and wrote the textbooks as they taught. I literally remember stenciling their lectures into textbooks in the summer for reading in the autumn. How I got into Psychopharmacology is still a mystery to me. I do not really know. I know that it is the fulfillment of what the Germans call Weltanschauung, arising out of my preoccupation with modern physics. I remember staring in awe at the cloud-chamber photographs of the early physicists the pull of particles. It was extraordinary. They held the mystery of the forces of which held the universe together. I went from physics to physical chemistry, from physical chemistry to the study of monomolecular films and on to medical school at St. Mary's in London where I was in the company of three giants. One was Alexander Fleming,

the discoverer of penicillin, who taught me bacteriology; the other figure was my Dean, Sir Charles Wilson, also later Lord Moran physician to Churchill and the third was Sir Almroth-Wright the great neurologist, discoverer of the typhus vaccine. Somehow the bridge to psychopharmacology was molecular recognition in immunology. I became very interested in the immune system, and very early on began to regard the immune system as a sort of liquid brain, a tissue, which has memory, learns from experience very much like the tissue we carry in our skull. So I got from physical chemistry to immunology and to psychiatry, which became a deep interest. My father was a distinguished physician in Lithuania and directed my reading. He directed my reading towards the writings of Paul Ehrlich, towards psychiatry, psychoanalysis, Freud and so on. Somehow there seemed to be a way of linking the economy of the tissue of the body to the economy, which goes on between people; to link the society within the skin to the society outside the skin. So I began to consider deeply, from the beginning the linking of the systems within the body to the systems outside the body. I could not make the break because we had no real basis of the knowledge of the biological substrate of mental processes. There was no link available nor was I equipped to do that, because my mathematics was poor. So, I didn't know what to do about it except to observe the phenomena. There, we were very fortunate at St. Mary's hospital where I studied because we had wonderful lecture demonstrations on the psychoses. We had a wonderful collection of mental hospitals in which I visited frequently; and I became absolutely fascinated by the phenomena of mental disorder which I saw in mental hospitals.

FS: Joel, can I interrupt you for a minute. You mentioned that you were at St. Mary's Hospital in London. I assume this was before you became the head of the first Department of Experimental Psychiatry in Birmingham.

JE: That came later. I was in Pharmacology at the time. I had gone to medical school at St. Mary's Hospital, London and was working in the Department of Pharmacology. Then, to make it very brief I had followed my chief and friend Alistair Frazer to found the Department of Pharmacology in Birmingham where I backed into Psychopharmacology. It was not driven; it was much more a bumping into phenomena which didn't make any sense and which in some way had to be conjoined. And in that department, in my early work, I was very intrigued by membrane cell surfaces and so on. Alistair Frazer was interested in fat absorption and not the nervous system; he was interested in chylomicron, a particle which appears in the blood after a fatty meal, and the

architecture of that particle. He gave me the task to find out what makes that particle and find what the covering of that particle is which keeps it, emulsified. So I was forced to look at a lipoprotein. I went from there on to the study of the lipoprotein, which is ubiquitous in the nervous system, myelin. We used x-ray diffraction following the wonderful work of Frank Schmitt from St. Louis to study the crystal structure of living membranes. We were, I believe, the first to study living myelin in the living cell. We constructed a cell which allowed us to irrigate a sciatic frog and test the viability of a segment while shooting x-rays through it and getting crystal picture of myelin; seeing the living, liquid structure alter slightly but in a predictable way as a result of ether drying and so on. So, I was edging into the brain by creeping-up the myelin sheath. That is how I got into the brain. At the same time we were beginning to work on the distribution of enzyme systems, particularly the choline-esterases, in the brain. In watching the maturation of the nervous system, and the distribution of enzymes in the maturing of the system we found that some areas are rich in choline-esterases. . By that time I was already deeply into Neurochemistry; I had finally found a way to get into the field. At about the same time, we are still talking of the 1940's, probably about 1948, '49 or possibly 1950, '51, before the discovery of chlorpromazine, Jean Delay came to London and gave a talk on catatonic stupor. I went to the lecture and was deeply impressed by the syndrome of the catatonic state which was common in mental hospitals at the time. We began to study the effects of Amytal (amobarbital), amphetamine and then Myanesin (mephenesin) that just came out, on this syndrome. It became quite clear that the two drugs had different effects. Amytal like an Andersen fairy tale, brought patients out of their stupor; they began to talk, recognize their relatives, ate their meal with relatives on Sunday and so on. Amphetamine drove these people deeply into stupor and Myanesin relaxed their muscle but did not affect speech. So you had a principle of a selectivity of drugs on the syndrome that alerted me to the fact that maybe we are dealing in catatonic stupor with a state of hyper-arousal, which is muted by Amytal and enhanced by amphetamine.

FS: It is overwhelming listening to the scope of your research interests. You started off with physical chemistry, then, went into chemistry, then into pharmacology and all the way to the clinic. You have in a very beautiful way integrated basic and clinical disciplines.

JE: I was beginning to do it at that time.

FS: This is in Birmingham.

JE: We are in Birmingham.

FS: In the first Department of Experimental Psychiatry?

JE: No, no, that came a little later. Why did it come? Because the university asked us what on earth we were doing? What is this strange field, what do you call it? And we said that we were working on “drugs and the mind”. Drugs and the mind, not the brain! The Mind! And, that became known as the Drugs and the Mind program. Then fate knocks on my window again. There was a department, a small obscure department on Mental Diseases Research which was loose in structure, administered from the Dean’s office that came under the Department of Pharmacology and I became head of it. Suddenly had two rooms and a lab to work in and then came a wonderful opportunity of Philip Bradley coming to my lab. You see, there was a base in chemistry in our work that was bridging across to the clinic but there was nothing in-between, to help you to study pharmacological intervention in the living conscious animal. So I discussed our task with Philip and we decided the first thing we must do is develop a technique, which would allow us to study the electrical activity of the brain in the conscious animal. It took Philip nine months to work out the technique. It was a very elegant technique of implanting electrodes into the cortex and sub-cortex in an intact animal, then bringing the electrodes out in the back of the animal and attaching a little plug to the electrodes that the animal could be plugged in the electrical recorder that would record the electrical activity in the brain of the moving alert animal.

FS: Well Joel, I see a connection here to my teacher in Zurich, W.R. Hess.

JE: My goodness, yes, indeed.

FS: Did you know him?

JE: No, I did not know him. So, that was the bridge between Neurochemistry and the Clinic, the cat’s electrophysiology. Then came the moment when I could compound the whole thing into a program which I showed the Rockefeller foundation when they came to see me. What I showed was that there was a connection between neurochemistry, electrophysiology in the conscious animal and behavior in patients.

FS: When was that?

JE: This was still two years before the discovery of chlorpromazine. And then Alastair Frazer supported me and said 'why don't you create a department for this field. What shall we call it?' And I had experimented with the term "experimental psychiatry" in my head for some six months; an experimental department which brings experiments to psychiatry, and I called the department, Department of Experimental Psychiatry. The small department was created in 1951 and I still remember the day when it happened. I was an intern in Norwich State Hospital at the time and in the list of interns and staff outside the superintendent's office, I was at the very bottom: Intern, Joel Elkes. When I came into Dr. Kettle, the superintendent's office, with the copy of a telegram which I'd just received from Birmingham that I had been appointed Professor of Experimental Psychiatry, he slapped his thigh and said 'My God, that's the fastest promotion I've ever seen at this hospital'. This is a true story. So I suddenly had a Department. of Experimental Psychiatry, which I believe was the first one in the world.

FS: It was the first one.

JE: Then, one day, Dr. Thrower, who was the clinical director of a pharmaceutical company, walked into my office and said: "this is not a routine visit." Then, he carefully unlocked his briefcase and gave me the copy of a paper by Delay and Deniker and said "this is astonishing". And he also said, "yes, that's why, I am here. We have got the patent in England for Largactil (chlorpromazine) and would you carry out a controlled trial?" So, I went to Charmian, my wife, who was given the responsibility of organizing the trial and make it work. We worked at the same mental hospital in a small research room and in that room we carried out the study of Thorazine (chlorpromazine) on 27 patients. I still remember walking into the boardroom at the end of the trial; the papers were on the table, the code was broken and the numbers went on the board. It became very clear that in 7 patients out of the 27, there was striking improvement on the drug and striking relapse on the placebo. Suddenly we were in Psychopharmacology! That's how I got into Psychopharmacology. I've given you the outline of this torturous past which led me to Psychopharmacology; the steps on the way were very, very unpredictable. I didn't know what I would bump into next.

FS: Joel, this is absolutely amazing how you covered such a scope from physical chemistry to neurochemistry to electrophysiology to psychopharmacology and to clinical psychiatry.

JE: Well.... .

FS: This was Birmingham and I guess that the next big step was when you met Seymour Kety and he invited you to come to the US.

JE: Yes. Then, I started commuting and exchanging information. I remember particularly Hy Denber coming over.

FS: This was in 1957?

JE: Before that. I remember being in the States; Smith Kline and French arranged for a meeting between Seymour Kety and myself. And I come into the lab and Seymour Kety was very busy. Shining, vibrant Seymour comes out and when he sees me his face falls saying with every gesture, “Oh, God, not another visitor” kind of thing. Then we go out to lunch, we talk and we go on talking, and it goes on and on and on... Seymour tells me of his dreams; he was just going from Philadelphia to the NIMH as director of the intramural program of the NIMH and I was just going to Birmingham to assume the Chair of Experimental Psychiatry in Birmingham. And we compared notes. We dreamt of the future of psychiatry and the future of research. Seymour was a prince of a man, a remarkable person of vision, clarity, integrity, and enormous talent. I think he should have stayed with the opening up of cerebral circulation and get the Nobel. Then Seymour and Bob Cohen were talking about the Laboratory of Clinical Science at the Institute.

FS: Was Kety chief of the Laboratory of Clinical Science?

JE: No, no, he was head, scientific director of NIMH.

JE: And he asked me to head-up the Laboratory of Clinical Science. I was so torn, at that time because the University, the Rockefeller Foundation and Medical Research Council in the UK had done a great deal for me so that I could not bring myself to move from Birmingham, and I said, no, I can't come. Then, a year later Seymour calls me up, and says, “Joel, I offered you the best job I've had; it was so good that I took it myself”. And he stepped-down from his position as scientific director of the Institute and became director of the Laboratory of Clinical Science. But he kept on talking to me in Birmingham and told me that there was a building available at St. Elizabeths', the William Alanson White building and he offered to refurbish it, to build labs. They

sent me plans to Birmingham, and catalogs of equipment and sitting in my little office in Birmingham I designed what were to become my labs in the William Alanson White building.

FS: Joel, I remember that building from the time when I was a post-doctoral fellow with Brodie and we had discovered, desmethylinipramine (DMI,) the secondary amine metabolite of imipramine. There was a fellow at St. Elizabeths' who was with you and conducted the clinical trial with it. His name was Freyhan.

JE: Freyhan, Fritz. I remember standing in front of the William Alanson White building when I arrived to Washington, looking up. It was a five-story building and I said to myself, my God, how do we make a community in this building? How do we build a community where we manage to fashion a science which is trans-disciplinary in nature and put a team into one head, if you see what I mean. How could we train people who are experts in several disciplines in this building and build a bridge between them. And I think we managed to do this; it was an extraordinary community in extraordinary times. We had people there working on frog brain and we had people working on enzymology. We had people working on the relation of metabolism and behavior and we had people doing clinical trials, like Freyhan, Hordern and others.

FS: Maybe Joel we're getting close in time to the inception of the ACNP now.

JE: Yes.

FS: If you could, perhaps talk about that and then we could go back later on to your research philosophy; to Joel the researcher and Joel the gardener. So, if you could tell us how the inception of the American College of Neuropsychopharmacology came about.

JE: There had been quiet discussions among some people about the need for a body where information and discoveries in psychopharmacology can be shared in a congenial way in a congenial environment. It started with Ted Rothman.

FS: Who?

JE: Ted Rothman, who unfortunately was not quite given his due. Ted Rothman, Jonathan Cole, Paul Hoch, myself and others convened a meeting in the Barbizon Plaza Hotel in New York to discuss how to advance Neuropsychopharmacology.



FS: This was in 1960?

JE: Yes. November 1960. There were twenty invited people and twenty guests. There, at that meeting, ways and means were being discussed and one suggestion was to form a college of Neuropsychopharmacology, a scientific society and incorporate it in Maryland. They did that and the constitution of the college was being prepared. And finally the first organizing meeting of the American College of Neuropsychopharmacology took place, I have a photograph of it here now, please see us eating dinner.

FS: Joel, if you could go back a moment and tell us again about who you consider to be the key figures shaping the field of Neuropsychopharmacology.

JE: Well, there were so many excellent people and there were so many people active. But the key people I would think were Seymour Kety, Paul Hoch, the commissioner for mental health for the state of New York, extraordinarily active at that time and Jonathan Cole who had already formed the center, the Psychopharmacology Service Center in Washington.

FS: And of course you had in the basic sciences Bernard Brodie.

JE: In the basic sciences, a key figure was Brodie, no question.

FS: You know, Brodie's Laboratory of Chemical Pharmacology was truly a Mecca of Psychopharmacology. I could never understand why he didn't get the Nobel Prize.

JE: Yes, I agree.

FS: Two people from his lab got it, Julius Axelrod and Arvid Carlsson. And Brodie who was really the father of biochemical pharmacology never got it. I don't know why.

JE: Politics is something I avoided continuously and it is due to my avoidance of politics that I've lived to 95!

FS: Then Joel, you got elected the first president of the ACNP. I had the pleasure of reading your lecture which you delivered when you were the first president. In it you defined the place of Neuropsychopharmacology and you gave an identity to the new science. And you said "Like a modern Rosetta Stone, psychopharmacology holds the key to much that is puzzling today. It

provides the key to three languages: the nervous system, the endocrine system and the immune system.” Well, Joel, I would love if you could elaborate a little bit on these beautiful concepts that you developed.

JE: Well, I feel that in the ‘60’s, there was a lot of fluidity and mobility in the field, and crossing over into disciplines there was an emerging understanding that there are four footings of the new discipline: neurochemistry, which was maturing so to speak because we did not have anything more in neurochemistry than written in Thudichum, electrophysiology, animal behavior and clinical trials. These were the four footings, which I saw as essential elements of any psychopharmacological enterprise worth its name. At the end of that meeting we created the committees which still exist in the ACNP. We also created study groups on various subjects.

FS: That was lovely, your idea of small study groups. I remember attending the Annual ACNP meeting as a post-doctoral fellow when we met in bedrooms.

JE: That’s right.

FS: Could you talk a little bit more about your idea of study groups?

JE: The idea was to select people from different discipline into small groups and give them the opportunity to talk to each other. That’s very simple and it developed very, very well. Study groups led to a sense of scholarship identity, of owning certain areas of psychopharmacology. And, it worked. I think I’ll read to you that I said at the time: “It is not uncommon for any of us to be told that psychopharmacology is not a science and that it would do well to emulate the precision of older and more established disciplines. Such statements portray a lack of understanding for the special demands made by psychopharmacology upon the fields, which compound it. From my own part, I draw comfort and firm conviction from the history of our group. For, I know of no other branch of science which, like a good plow on a spring day, has tilled as many areas as neurobiology.”

FS: Beautiful. Keep on going.

JE: “To have in a mere decade questioned the concept of synaptic transmission in the central nervous system; to have emphasized compartmentalization and regionalization of chemical processes in the unit cell and in the brain; to have focused on the interaction of hormone and

chemical process within the brain; to have given us tools for the study of chemical basis of learning and temporary connection formation; to have emphasized the dependence of pharmacological response on its situational and social setting; to have compelled a hard look at the semantics of psychiatric diagnosis, description and communication; to have resuscitated, the oldest of all remedies: the placebo response for careful scrutiny; to have provided potential methods for the study of language in relation to the functional state of the brain; and to have encouraged the biochemist, physiologist, psychologist, clinician, and the mathematician and communications engineer to join forces at bench level is no mean achievement for a young science. That a chemical text should carry the imprint of experience and partake in its growth in no way invalidates the study of symbols and the roles among symbols which keep us going, changing, evolving, and human.. Thus, though moving cautiously, psychopharmacology is still protesting; yet, in so doing it is for the first time compelling the physical and chemical sciences to look behavior in the face, and thus enriching both. If there be discomfiture in this encounter it is hardly surprising, for it is in this discomfiture that there may well lie the germ of a new science.”

FS: Well Joel, these are memorable words spoken by you as the first president of the ACNP. I wonder, what role did, the ACNP play, in your own work. And how do you feel the ACNP has shaped the field over the next years?

JE: I can only tell you that I looked forward to the excitement of the next meeting of the ACNP, year by year, as a boy looks to toy books. It was an extraordinary feeling. I remember in October and November, oh my God, ACNP, is coming in December and how I was looking forward to it. Why? Because I found that among the colleagues there, languages developing that we could speak and understand each other. I could find sometimes, totally new, totally new areas opening up suddenly in a meeting by a presentation. I found extraordinary contact and enrichment and I felt home. The ACNP was my home! I used to go there regularly not only to listen to the stories, the same stories, told by the same people, with the same Élan; there was also a feeling of great seriousness about the ACNP. This was a very serious body. It meant its business; it created committees, which did their work. It created rules, which were followed. It gave guidance, which has guided us to this day in our work. I think it was to me, a home base that was so absolutely necessary, because we had no moorings, a wonderful organization that grew and grew and grew. I remember in the early days when I was still in Birmingham that Ernst Rothlin and Mrs. Rothlin

came to stay with us and we discussed, with Bradley's and Dr. Mayer-Gross' participation, who was working with me at the time, the desirability of a journal in psychopharmacology and the desirability of an international association in psychopharmacology, which became the International College, the Collegium Internationale Neuro-Psychopharmacologicum. Mayer-Gross spoke to Jung of Springer Verlag and they were interested in founding a journal. And, then, we brought in Abe Wikler, a very shy and modest man, a seminal figure in psychopharmacology, as editor. His book on the relationship between pharmacology and psychiatry was one of the first real texts in the field. I also remember the wonderful time when suddenly the yellow journal, *Psychopharmacologia*, our journal, landed on my desk. The World Health Organization became very interested in psychopharmacology and asked me to convene a small group of people in Geneva and we had a very good discussion. I wrote the initial draft of the working paper. Then, I remember getting a letter from the head of the Drug Programs of the World Health Organization, Dr. Wolf. The letter said you have given joy to a man who gets breathless as he reads your paper. And I didn't know what he meant until I got to Geneva and found that Abe Wikler was dying from cardiac failure. When I was visiting him he hardly recognized me; he was on oxygen, his breathing at the time was terminal.

FS: Well, Joel, you have been the first president of the ACNP and you have given a new identity to the science of neuropsychopharmacology. Let's go back a little bit for a little while to the ACNP and to the early meetings in Puerto Rico. If I remember correctly, we met at the beginning at the Sheraton and then we moved the meetings to the Caribe Hilton.

JE: Yes.

FS: If you could talk about the early days of the meetings in Puerto Rico and the people who were involved in running the organization and any fond memories you have.

JE: My fondest memory is simple the memory of Puerto Rico. I love the sun and I think what brought us to Puerto Rico was the love of the sun. We had wonderful times there and I remember particularly the meetings that Jonathan Cole and Oakley Ray organized later. With time Oakley Ray became the giant of the organization.

FS: You know I was the one who brought Oakley in as secretary-treasurer when I was president of the ACNP after Al DiMascio passed away. At a council meeting in New York, Larry Stein

suggested that when I go back to Nashville I should ask Oakley Ray to run for secretary of the ACNP. Oakley agreed, ran and got elected and I think the ACNP has never been the same.

JE: Absolutely. Oakley was the spirit of the ACNP.

FS: I agree with you.

JE: There might be a rambunctious way about him but at the bottom of it there was dignity, there was grace, there was decorum. I think that he really was a remarkable man.

FS: Yes, I couldn't agree more with you. Well Joel, of all the people who were there with you were people like Danny Freedman.....

JE: Danny Freedman. I remember that the first contact I had with Danny Freedman was at a seminar at Yale where I mentioned something about that schizophrenia may turn out to be a biochemical lesion of the upper brain stem. That is the word I used. And he, little fellow that he was with piercing eyes, came up to me and gripped my hand, and said, you said it Joel, you said it, with a kind of enthusiasm which I've never forgotten. And we've corresponded about this idea since.

FS: Well, we also had Leo Hollister, who is not with us anymore; do you want to say a few words about Leo? He was our president in the 1970's.

JE: He was a fine person, a fine person.

FS: And Morris Lipton.....

JE: Morris Lipton I knew very well. He came up from North Carolina.

FS: Chapel Hill.

JE: Yes. And I remember him doing a headstand in my living room. And Lou Lasagna, God, what a fellow.

FS: We had the Killam's, Keith and Eva.

JE: I knew them very well. I knew them back in Birmingham. One of my colleagues, Jim Hance, joined them. I saw Eva from meeting to meeting and then gradually she became ill and invalid in

a chair. But never, never did her spirits flag. They were a remarkable couple. They were very early in the field.

FS: And of course there was Dick Wittenborn.

JE: I knew him well. Dick Wittenborn was a very straightforward, honest, strong, strong man.

FS: Do you want to say anything about the flavor of the meetings in Puerto Rico?

JE: Only that they were extravaganzas, of a sort. I couldn't believe it that we could talk science in such company and in such a place. And then in the afternoon we were all in our swimsuits, walking around, talking and coming into the meetings in swimsuits very, very casual. I loved it!

FS: It is quite a change now from the early days when we met in bedrooms

JE: I remember the bedrooms. I remember particularly the hotel in Washington in which the first meeting took place, the Hotel on 16th street. All that I remember apart from the meeting was the short skirts and silk stockings that waitress' wore. I remember it to this day.

FS: Well, it is already late Joel and I'd like to talk about your research philosophy, the concept of the Rosetta Stone.....

JE: Oh, the Rosetta Stone.

FS: I think that this is such a beautiful concept. And it's not only beautiful but it's true! Joel, please talk a little bit about molecular communication.

JE: I will. In 1952 I gave a paper to a research association and I talked about that for neurotransmitters to be present enzymes should be present for their synthesis in destruction. I also said that enzymes should be responsive to enzyme inhibition and there should be a specific tissue response. Then I began to think of the concept of these molecules acting as transducers and transponders in the brain, facilitating communication. And I was struck by the fact that psychoactive drugs have peculiar properties of interaction with two or three neurotransmitters, and from the shared properties of psychoactive drugs and neurotransmitters came then the idea of psychopharmacology as a tool for understanding shared properties in molecules, leading to the concept of psychopharmacology as a Rosetta Stone for understanding the way that the brain

communicates inside itself. I talked earlier about communication of the society within the skin and the society without.

FS: Before we leave we have to talk about one other great contribution that you made. And this is the making of people. I wonder if you could talk about what you called the “gardening.”

JE: I called it gardening. Well I tried to create a climate of receptivity, understanding, excitement and tolerance for ideas, for new ideas. I tried to create a language which was understood and which could go across disciplines. Let me put it this way, the fact that we created a clinical neuropharmacology research center with basic science labs at St. Elizabeths’ where Floyd Bloom and Nino Salmoiraghi worked that this center was at St. Elizabeths’ where when you walked to the canteen to have your lunch, you saw a schizophrenic patient hallucinating under a tree, that is what I’m talking about.

FS: Joel, wasn’t Weil-Malherbe at St. Elizabeths’?

JE: Oh, yes, very much so. I brought him all the way from England.

FS: It was Montagu in Weil – Malherbe’s laboratory who reported in 1957 first on the presence of dopamine in the brain of several species, including man. Wasn’t Baldessarini from Harvard with you?

JE: Yes, and Sol Snyder, who had this wonderful career. He started as a resident. I think I could go through the list but it is rather long of people who came through the labs and who left their mark, everyone of them. They left their mark on me. But, I don’t think, we haven’t got the time for that.

FS: We’re now in the year 2008, Joel and the field, our field has gone predominantly molecular. During the last few years we have learned more and more about less and less and I think it’s time, to go back to your more holistic philosophy. I am wondering how you see the future will develop from now on?

JE: I see the future in linkages. Linkages! Linkages of the college with areas on which psychopharmacology clearly impinges but which remain undefined. I see linkages with

psychoimmunology; linkages with endocrinology and linkages with people who have an understanding of message transmission, with information engineers.

FS: And behavior.

JE: And behavior.

FS: You know it is remarkable, Joel, that every prototype of psychotropic drugs got discovered in the 1950s at a time when we used behavioral correlates as drug targets.

JE: Yes

FS: And now in the last fifty years we haven't discovered anything new.

JE: We are not looking in the right place.

FS: That's right.

JE: We are not looking in the right place.

FS: It's a very important message that you and I need to give to young people.

JE: Yes: Linkages, linkages and linkages.

FS: That's right. Say it again, Joel.

JE: Linkages!

FS: I think that molecular pharmacology has to become functional again.

JE: Yes, exactly.

FS: We have to go back to W. R. Hess.

JE: Yes.

FS: Well, Joel, the last topic which I wish to cover is your work in the arts; the importance of arts in medicine and healing.



JE: Well, thank you. That grows from a personal, very personal inclination. Let me put it this way. I ask myself why art? Why art? Why is art so powerful? Why does it influence people so profoundly? I suggest to you that Art is so powerful because it reaches into the realm of the “No Words”. Words are limited. Words create a little universe of the sound and the meaning in which to convey. It is what lies between words that make prose poetical. It is the exploration of the in-between which art allows. As you know, I paint. And my painting arises out of feeling, a profound sense of communication with nature. It is a direct, very direct communication. What you cannot express in words you can convey in art. We started for example in Louisville at the end of my career, a program for the arts and medicine. We employed painting, drama, poetry, prose, and humor. We had some very gifted young people working with us and we started working in areas of post-traumatic stress, in the Vietnam veterans. And I remember distinctly the occasion when an art therapist took a lump of clay and handed it to a patient who could not speak, who could not remember, who could not communicate and put it into his hand and said, “Tell me with this lump of clay.” And within twenty minutes that totally inexperienced young person fashioned a beautiful figure with another small figure draped across knees, like a Pieta and was excited and started talking about, “I didn’t kill that child. I didn’t kill that child. He just fell on my knees.” And went on and on about the time when he was there in the bush, in a native village. And he went on drawing, sculpting away until the last sculpture materialized, an angelic figure rising to Heaven. And it was all...When I saw that and we have it on film, I was convinced, my God, it goes much deeper than words. When I paint I start by staring at an object. I keep on staring at it and staring at it until I hear a conversation between the object and its ghosts. A stone will speak to a ghost of a stone and there is a conversation between mundane and the mysterious taking place. And then you put it down. It is a conversation between the light and the dark, the visible and invisible. The trees have always bright leaves against the dark trunk; there’s a tint of nature about them. I have some paintings, which bring back that happened to my family, but indirectly, indirectly. I have never yet painted a truly direct painting... I have one, actually, called the Mass Grave. Sticks of figures lie in a pit. But apart from that what I am saying is art goes where words do not go. Art leads you into a world which is magnificent and art is something which should be part of the substance of medicine because it is the substance of healing like this young man began to heal for the first time in seven years by having a piece of clay in his hands. So, there are many, many opportunities and at The Phipps Clinic at Hopkins when I was there we had an active art therapy

group. We had a very active art therapist, and Sally, my wife and I talk about it very often because Sally has much more experience than I have in art therapy and we hope to do something practical about it sometime.

FS: Well, Joel, I think this is a very unique part of your curriculum. If I remember correctly you created a program in Louisville on the arts and medicine.

JE: Yes. I did.

FS: Can you tell us a little bit about this before we close?

JE: I had a colleague in Louisville who worked with me and helped me create the program where therapy was applied as an accepted therapeutic modality for patients who are disturbed, who have fantasies, who have wild dreams and so on. We also gave students an opportunity to develop art as a hobby. They created art works. We had an exhibit every year of student works. We had readings of poetry, somebody wrote a novel etc. etc. etc. It was a magnificent program. It was part of a health awareness program for medical students. We thought, at Louisville, that it would give an opportunity for students to get to know themselves and each other. We introduced it at the beginning of the medical curriculum; before they became medical students, we invited them for a week, to come early and have an exposure to the opportunities that they all are heir to. They were segments on nutrition, exercise, meditation, training and awareness training, listening skills, small group work. We did this for a week before the medical school started. At the end of the week the Dean comes in and says, "Welcome to the medical school." And they have already had an exposure to aspects of medicine, which they otherwise would have missed. And that program went really extraordinary well. We continued it for fourteen years at Louisville. We carried-out some studies, but, unfortunately, didn't have the money to carry out a really good follow-up study. But, I know from an anecdotal, remembering how much the students valued this exposure.

FS: Well, Joel, we have covered a remarkable story in neuropsychopharmacology; your journey through the field from physical chemistry, to neurochemistry, to clinical pharmacology, to the integration of basic and clinical sciences, and to the creation of the ACNP. We talked about the major people who have moved the field. We have talked about Joel, the research scientist and physician, and Joel the gardener of people! We have talked about Joel and the arts and medicine and Joel the painter. How remarkable, Joel. We are looking forward now to the fiftieth anniversary

celebration in 2011 and I think you have inspired us for fifty years with your eloquence, your creativity and your undying curiosity. And for this, Joel, we thank you very, very much.

JE: Thank you very much for listening. This is a very special moment for me. I have really very little to add because there is such an enormous amount to say. I can only express my deepest gratitude, respect to the College for doing me the highest honor I received in my life. To give me the opportunity to be in the company of such wonderful people and participate in the growth of young people who came to the laboratory. We've all done well. We all keep on looking. We all have to hold lanterns- lanterns, which illuminate areas, which are still murky, poorly understood. Above all, I think, we have to create new alliances because the nature of our field compels us to choose and choose again people, from disparate and different fields. For example, the whole question of communication in the nervous system cries out for collaboration between neurophysiologists and psychologists, education experts, communication engineers, language-translation specialists and so on. And they don't know what we know! And we don't know what they know! And the knowledge has to come together by work at the bench and common new languages will evolve as we work together. So, we need alliances and alliances, even with strange fields; to be trans-disciplinarians; make it evident that this is a science like no other is, it has special characteristics of its own and will in time have earmarks by which it is known. It is not only molecular biology; it is not only electrophysiology; it is not only animal behavior; it is not only clinical syndromes. It is the conversation and the interaction between these areas, which matters and we must do all we can to enhance the conversation. This is what the college can do like no other organization nationally and internationally. We must bring people in, we can learn from them. We have an unusual opportunity as a College and we should move it as my wife Sally says: "move it, move it." I'm delighted to be here and share this with you. Thank you very much.

## 5 PAPERS

Two of Joel Elkes' publications were selected for inclusion in this volume: (1) Discussion: Prospects in psychiatric research, first published in JM Tammer's *Prospects in Psychiatric Research* (Oxford: Blackwell; 1952) and (2) The American College of Neurosychopharmacology: A note on its history and hopes for the future, first published in the *ACNP Bulletin* in 1962.

In the first Elkes outlines some ideas on the use of pharmacology in the study of mental organization. He takes up some neurochemical issues and the possible use of neurotransmitters familiar in the periphery as reference points for the study of central events. He defines some "simple desiderata" that he would like to see fulfilled by a substance claiming to act as a neurotransmitter in the central nervous system; and outlines the idea of families of neuroregulatory compounds which vary in density and distribution according to region and even in the same region. He also emphasizes the importance of interaction and balance between cell population carrying different receptors, a theme that draws on the demonstrated facilitatory (permissive) or inhibitory interaction between neurotransmitters at peripheral sites.

The second is a summary of Elkes' address at the end of his tenure as the first President of the American College of Neuropsychopharmacology.

## PAPER 8

**DISCUSSION: PROSPECTS IN PSYCHIATRIC RESEARCH****Joel Elkes**

Reprinted with the kind permission of Blackwell Science Ltd. from J.M. Tanner (ed.) *Prospects in Psychiatric Research* (pp. 126-135). Oxford, Blackwell Scientific Publications, 1952

The use of pharmacology in the study of mental organisation is inseparable from its use in the broader field of neurophysiology, and its contribution to psychiatry will be measured by its contribution to an understanding of the brain as an integrating, feeling and computing organ. The vast cell population and the continuous activity of the central nervous system militate against a convenient study of the relation of the part to the whole. Nevertheless, an ever-growing body of knowledge is rapidly leading to a much clearer understanding of the physiological basis of perception (Adrian 1948, 1952, Walter 1950) and to the recognition of some, as yet qualitative and approximate, relationships between cells and groups of cells within the central nervous system (Dempsey & Morison 1942, Jasper 1949, Magoun 1950). It is here, in the modification of individual cell function, and in the relationship between cells, that pharmacological tools may find their application. Their discriminate use in systems of varying complexity may be helpful in an understanding of the organisation of these systems.

It may be useful to think in terms of some broad and common theoretical pathways by which chemical agents may exert their effect on the central nervous system. They may, for example, act by modifying the energy metabolism of the cell along some selective lines, or alternatively, by altering the ionic or humoral environment of neurones either generally, or at some specific sites. The distinction between the power-economy of the cell, the integrity and function of its membrane, and the possible local elaboration of highly specific humoral agents, is a distinction which is conveniently made in the mind; it is quite unlikely to be made in the cell, where the several processes overlap, and are mutually complementary and interdependent. Thus energy metabolism is almost certainly related to membrane integrity, and, as is well known, membrane permeability, can be profoundly altered by specific neurohumoral agents, e. g. acetylcholine. The uses of these arbitrary distinctions lie principally in defining approach, and field of work. There would appear to be some disproportion of data at present available in these three areas. For example, a great deal is known of the intermediate energy metabolism of brain tissue (Himwich 1951), yet the evidence of the precise effects of chemical agents upon its various stages remains incomplete. Similarly, our recent understanding of conditions obtaining at the neurone membrane (Hodgkin 1950, Keynes 1951) poses many a pressing pharmacological problem. The position of potential humoral synaptic transmitters in the central nervous system is peculiar. Abundant data are available on neurohumoral trans-

mission at such peripheral sites as autonomic ganglia, secretory cells, and smooth and skeletal muscle; the mode of action of various drugs at these sites has been extensively studied. Yet the relevance or otherwise of these findings to the central nervous system can only be determined in the light of further information obtained from, and within the central nervous system itself. Such information is now gradually coming forward.

There are certain simple desiderata which one would like to see fulfilled by a substance claiming a transmitter role in the central nervous system. Four of these come to mind. Firstly, the substance should be present in the central nervous system; it should also vary in quantity with the functional state, and should be identifiable by sensitive, reliable and unequivocal tests. Secondly, there should be enzymes present, responsible both for the synthesis and the breakdown of the substance in question. Thirdly, the blocking of these enzymes by specific inhibitors should result in effects related to either lack or accumulation of the hypothetical transmitter. Fourthly, the application of the substance to the central nervous system by either local or systemic routes should have demonstrable effects on the function of the tissue.

It is perhaps natural that the attempted identification of central neurohumoral mediators should have begun with acetylcholine. With certain important reservations, this substance appears to satisfy the above criteria. It is present in the central nervous system, and, as has been shown by Richter and Crossland (1949), can vary in concentration with the functional state of the animal. Thus, it is high in anaesthesia and in sleep, and diminished in excitement. Again, enzyme systems both for synthesis and breakdown have been identified; these are choline-acetylase, and the so-called specific and non-specific ("true" and "pseudo") cholinesterases. In their important studies, Feldberg and Vogt (1948), and, later, Feldberg, Harris and Lin (1951) have demonstrated a curiously uneven distribution of acetylcholine synthesising power throughout the central nervous system. Thus, for example, the anterior roots are rich in the enzyme, though the pyramidal tracts are poor, and whereas the enzyme is low in the sensory roots, it is abundant in the gracile and cuneate nuclei. This at least suggests the possible existence of cholinergic as well as non-cholinergic neurones within the central nervous system. A universal transmitter role for acetylcholine would thus seem unlikely (Feldberg 1950) although there can be no doubt of its activity at some neurones.

This activity is borne out by a third group of data concerning the central effects of cholinesterase inhibitors which appear to be attributable to the accumulation of acetylcholine at some central synapses. The number of such inhibitors is steadily increasing, their specificity for the enzyme receptors is high, and their effective concentration correspondingly low (in some instances as low as one in ten billion). They can be reversible in their attachment to the enzyme (for example Physostigmine or Neostigmine), irreversible (DFP; Adrian, Feldberg & Kilby 1947, Rowntree, Nevin & Wilson 1950) or partly reversible (TEPP; Hobbiger 1951); they can have a predilection for the "true" cholinesterase (e. g. Nu 1950; Hawkins & Mendel 1949) or, the non-specific pseudo cholinesterase (e. g. TOCP; Earl and Thompson 1952). It is important, incidentally, to distinguish between these two enzymes. Most emphasis has hitherto been laid on the "true" cholinesterase of the brain. There is little doubt, however, from our own work and work in other laboratories (Burgen & Chipman 1951), of the existence of the non-specific "pseudo" enzyme in some areas of the central nervous system. Just what roles it, and its unknown substrate play in function, further specific inhibition studies may be expected to show.

The fourth line of evidence concerns the effects of local application of acetylcholine to the central nervous system, or its administration by a selected vascular route. This approach has a

long and varied history; and the evidence has been admirably summarised in a recent review (Feldberg 1950). Added acetylcholine can undoubtedly exert *some* influence on function in the central nervous system. But, again, one is impressed by the weight of negative evidence, suggesting that substances other than acetylcholine, of equally wide or wider distribution, may play a complementary part.

One's mind, of course, turns to *noradrenaline* and *adrenaline*. It is of great interest that *noradrenaline* has recently been identified in the hypothalamus and the medial thalamic nuclei of the cat (Vogt 1952), though we know, as yet, nothing of its synthesis, its role, or its possible breakdown by amine oxidase (Burn 1952) in these regions. Similarly the central effects of inhibitors of amine oxidase such as ephedrine (Gaddum & Kwiatkowski 1938) require much fuller study. Again, the extremely interesting work on the effects of addition of *adrenaline* to perfusates of the superior cervical ganglion (Bülbring 1944) or the spinal cord (Bülbring & Burn 1941), suggesting an interplay between acetylcholine and *adrenaline*, invites similar experiments at higher levels of the central nervous system. There are also curious structural affinities between *nor-adrenaline*, *adrenaline*, ephedrine, amphetamine, methylamphetamine and mescaline; and our most powerful "phantasticum", lysergic acid diethylamide (LSD-25; Stoll 1947), acting in doses of 30 to 50 micrograms by mouth in man, is a synthetic ergot derivative, ergot being a parent substance of some *adrenaline*-blocking agents. There is thus no lack of suggestive evidence. Nevertheless, care has to be exercised if one is to avoid a facile carrying-over of interpretation from one system to another, and it is wise to stick to some of the desiderata mentioned earlier. In the case of *noradrenaline* they remain unfulfilled, and only further experiment will determine its role, or the possible role of the vasodilator substance of nervous origin recently studied by Holton and Holton (1952).

One cannot help wondering whether one would not be nearer the truth if, instead of thinking in purely unitary terms, one began to think in terms of groups or families of compounds, possibly evolved as variants of original parent substances. There may be esters other than acetylcholine and amines other than *nor-adrenaline* or *adrenaline* taking part in a continuous turnover, regulated by the activity of corresponding enzymes. The balance may be delicate, and the effects of slight changes in molecular configuration of a substance profound. One need not go further than the steroids to seek an analogy of a family of compounds, or the effects of "local hormones" (Burn 1950) on function to see just how fine the balance between chemically mediated excitation and inhibition can be.

Basic information on the enzyme constitution of neurones thus becomes one pre-requisite before we can hope to take the study of the action of drugs on the central nervous system from a descriptive and empirical level towards a more precise understanding. Certain enzymes may be characteristic of certain types of neurones or glia, and magnitude of number of elements in the central nervous system need not necessarily reflect multitude and variation in kind. It is, in fact, not unlikely that the nervous system may be built on a relatively simple plan, and that variation and distribution of a limited number of types may make for apparent complexity. Thus a particular type of neurone may be scattered at random throughout a region, or be condensed into sheets, clusters or bundles in topographically close or in widely separated areas. The pharmacological susceptibilities of a region will be those of its dominant cell population, and of cells "impinging" (Feldberg 1950) upon it from nearby, or from afar. To talk of "levels" of action, as for example of predominant cortical, thalamic, hypothalamic effects, although in some instances perhaps empirically true, is apt to be misleading. Delicate shifts of balance between various cell groups would seem more likely.

There are certain advantages in assuming the existence of neurohumoral substances in the central nervous system. These lie in the fact that a good deal is known of the action of some chemical mediators at peripheral sites, and that the properties of some drugs can be partly or mainly ascribed to highly specific effects on the metabolism and effectiveness of local transmitters at these sites. The action of the anticholinesterase substances has already been mentioned. Drugs antagonising the peripheral effects of acetylcholine, adrenaline and histamine furnish further examples. Thus atropine blocks acetylcholine at autonomic nerve endings, and the curariform agents block transmission at the motor end plate; Dibenamine (Nickerson 1949) antagonises the peripheral effects of adrenaline, and the antihistamines the local effects of histamine. It is perhaps of interest that atropine (and, to a lesser extent, some of the antihistamine compounds) exert a protective effect against DFP and TEPP poisoning, and that in the case of atropine vis-à-vis TEPP the evidence strongly suggests a central effect (Douglas & Matthews 1952). The ill-defined nature of the central effects of such compounds need not deter one from closer scrutiny for their merit may not so much lie in these actions, as in the possession of an overriding property which, by slow trial and error, may lead to a better understanding of these central effects and the enhancement of similar effects by possible analogues. The possession of a few pharmacological precision tools may thus be helpful in interpreting the less definite, composite, statistical states so common in the central nervous system, and also aid an understanding of the mode of action of other drugs whose properties are less apparent. Cross-relationships between actions are constantly coming to light. The recent development of drugs used in the treatment of Parkinsonism from some antihistamine compounds (Bovet, Durel & Longo 1950) furnishes but one example of this trend.

It is with such chemical and physicochemical considerations in mind that one should also re-examine the central relaxing substances (e. g. mephensin; Henneman, Kaplan & Unna 1949) the barbiturates, analgesics and anticonvulsants. Similarly the central effects of the ganglion-blocking agents (Paton & Zaimis 1951) and their analogues are only slightly known, and may be full of interest.

The above drugs, though exerting some central effects, are hardly characterised by selective effects on higher mental function. It is to these latter substances that the attention of the psychiatrist inevitably turns. The origin and properties of such agents is varied, and the mere mention of alcohol, some of the volatile anaesthetics, the barbiturates, morphia, cocaine, cannabis, amphetamine, mescaline and, lately, the very powerful diethylamide of lysergic acid (LSD-25), will indicate the scope of the problem. The florid symptoms produced by some members of this group (particularly the so-called "phantastica", e. g. mescaline, cannabis, cocaine and LSD-25), despite the remarkable penetration and insight of some workers, have not always encouraged a careful and quantitative approach. The symptoms are well known, and need not detain us: disturbances in sensory perception, body image, time sense, affect, and in some instances autonomic and motor function, set in a state of consciousness which, though fluctuating, allows detailed self-observation; the lack of gross disturbances of speech despite interference with the normal imagery of language – all these sufficiently resemble some symptoms of the major psychoses to challenge further use of such drugs in a study of higher mental organisation. It is, however, well to remember the limitations of such an approach as well as its conceivable promise. To argue from the results of intoxication experiments to the aetiology of mental disorder is totally unjustified by the available facts.



It clearly reflects our present state of ignorance that we know almost as little of the mode of action of these phantastica as, for example, of the analgesics. Knowledge usually depends on method, and here at least, there is some promise of progress in the foreseeable future.

What are these methods? The relevance of the purely biochemical approach has already been stressed and, no doubt, will be stressed elsewhere during this meeting. The enzyme constitution of heterogeneous cell and fibre populations may slowly yield to microchemical and histochemical techniques. Possible effects of drugs on enzyme systems may be assessed just as directly from small tissue samples (Holter & Linderström-Lang 1951) or tissue culture (Abood, Cavanaugh, Tschirgi & Gerard 1951), as indirectly from the accumulation of one or other of the metabolites in tissue fluids. The use of radioactive tracer techniques, especially if coupled with methods recently developed for studying cerebral circulation (Schmidt 1950) will no doubt make their contribution to the basic biochemical data.

But the fact that interneuronal events are temporally related makes a fuller understanding of these time-relationships indispensable, and it is here that the rapid recording methods of the electrophysiologist become invaluable in a study of drug action. Microelectrode techniques (Brock, Coombs and Eccles 1951), recording from single or a limited number of neurones can be used alongside electroencephalographic methods furnishing data on the overall electrical activity of large cell populations. In animals, cortical and stereotactically placed sub-cortical electrodes may be employed, either in acute experiments, or permanently implanted for work with the conscious, unrestrained preparation. Dr. P.B. Bradley in our laboratory has recently developed such a technique. Up to ten electrodes can be implanted into the skull of a cat, the leads being brought out through the skin of the shoulder area and attached to a miniature multiple socket, carried by the animal in a small harness. It is thus possible to plug in directly into the various cortical and subcortical leads. With suitable precautions sepsis in these chronic preparations can be avoided, and animals have been kept in good condition for periods up to one year, though, more usually, they are killed after three months to check electrode placement. Observations in the conscious animal are usually carried out in a constant-environment chamber, which makes possible simultaneous recording of behaviour and electrical activity. The effect of sensory, (for example rhythmic photic), stimulation can also be studied. Drugs can be applied singly or in combination, and the vitiating effect of anaesthetics is completely avoided. The information thus obtained is, of course, complementary to that yielded by acute experiments, where chemical agents may be applied to the brain by the systemic or carotid routes, or by direct local microinjection into selected areas. Interruption of pathways, and destruction of isolated cell groups are further procedures designed to reduce the number of variables in such studies.

Animal behaviour offers another large and useful field, and the effects of chemical agents on basic activities such as sleep, food, and sexual habit, on the processes of discrimination and learning, on conflict and conditioned behaviour (Masserman 1943) invite further detailed study. Here again a combination of experimentally produced anatomical and biochemical lesions may be helpful, and parallel studies on the electrical activity of the brain in such experimentally induced behaviour disorders, or the effects of electrical stimulation upon them, may add further information.

Whatever data animal experiments may yield, however, must be regarded as only preparatory, and complementary to data obtained in man, where subjective sensations communicated by means of speech add a fund of information inaccessible in the animal experiment. Two groups of observations are relevant here. The first concerns the effects of some drugs on men-

tal function in normal subjects; the second the modification of abnormal mental function in patients by pharmacological means. The gross effects of the "phantastica" on normal volunteers are well known, and well documented (see Mayer-Gross 1951). Although there is little doubt that some effects are peculiar to some drugs, the final picture of intoxication depends upon the personality of the subject. I do not know that one need always go to full intoxication in such pharmacodynamic studies. It may perhaps be equally useful to work with the early symptoms and to see whether they can be enhanced or arrested by some controlled chemical or physical means. We have recently begun to record in some detail the illusions (of colour, pattern and movement) induced by rhythmic photic stimulation by white light at frequencies from 4 to 24 cycles per second, and the possible effects of some drugs upon them. Subjective sensations at each frequency are sound-recorded, transcribed, and the transcript analysed subsequently for relevant elements. Our experience with this method is as yet very limited, and because of its time-consuming nature, it may be a long time before sufficient data are ready for review and assessment. Nevertheless, even at this stage, one cannot help noticing the curious resemblance between the coloured, fine, ordered geometrical patterns reported as visual hallucinations in mescal intoxication, and the patterns induced by some frequencies of photic stimulation in normal subjects in the absence of any medication. Both phenomena may perhaps represent a shift in the time base, (that is in the "beat" of some elements of the visual pathway), the shift being induced, in one instance, by rhythmic stimulation of the visual fields, and in the other by some selective interference with a cycle of chemical events in certain neurones. Whether such changes are related to recent evidence concerning a triple pathway along the visual system (Clark 1941, Chang 1951) only future experiment can tell.

The second group of data concerns the effects of some drugs on mental and somatic function in clinical material. The amytal interview, the ether abreaction, the effect of dextro-amphetamine on mood and appetite are simple and well-known examples of such effects. The remarkable increase in accessibility brought about by small doses of intravenous sodium amytal in long-standing cases of catatonic stupor forms a useful starting point for pharmacological investigations of this kind. Dr. Charmian Elkes in our laboratory has recently had occasion to compare the effects of intravenously administered sodium amytal, amphetamine, and mephesisin in nine cases of catatonic stupor, who were selected according to a number of criteria out of an original group of 23 patients. Amytal increased accessibility, as shown both in terms of verbal productivity and of drawing; there seemed to be a better correlation between this increase of accessibility and foot temperature than between accessibility and muscle tone (as measured in the flexors of the elbow by a simple weighting device). Optimum psychomotor effect was only rarely accompanied by muscular relaxation. Amphetamine decreased accessibility, a finding unlike its more common effects in control material. Mephesisin regularly reduced muscle tone (i. e. the weighting figures) without appreciably altering either accessibility or foot temperature.

What developments such transient effects of drugs on normal and abnormal mental function foreshadow, it is difficult to say at this stage; but no one will question the challenge implicit in such simple facts. The critical study of familiar chemical agents, and of deliberately fashioned analogues, (used either singly, or in combination, so as to emphasise or attenuate some particular property) offers an inviting field to physiologist, psychologist and physician alike. Problems of perception, of affect, and of the cognitive, adaptive, and integrative functions commonly comprised by the term "ego" may perhaps be aided by the study of the effects of such agents. As yet we know little of the chemical basis of learning, remembering and for-

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getting; and it is not unlikely that both electroconvulsive therapy and leucotomy will in time yield to more discriminate chemical means. Drugs have begun to find their use in diagnosis and therapy, but their real value will keep step with their use as research tools. Our understanding of their action will depend on our understanding of the coding and cipher employed by the brain in the elaboration and storage of its patterns, and yet such understanding may be enhanced and supported by the very agents we employ. Perhaps time may turn out to be the denominator shared by brain patterns and the physicochemical activities of its constituent neurones.

Certainly for the present the gaps far exceed the body of knowledge. Looking at this field, one is rather reminded of Cézanne's later paintings, where, shining through surfaces of subtle and delicate colour, there are large areas of bare canvas. He is reputed to have said that he left them bare because he was not certain. Yet they form part of the picture. It is as good to wonder as to explain.

## THE AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY: A NOTE ON ITS HISTORY, AND HOPES FOR THE FUTURE

Joel Elkes

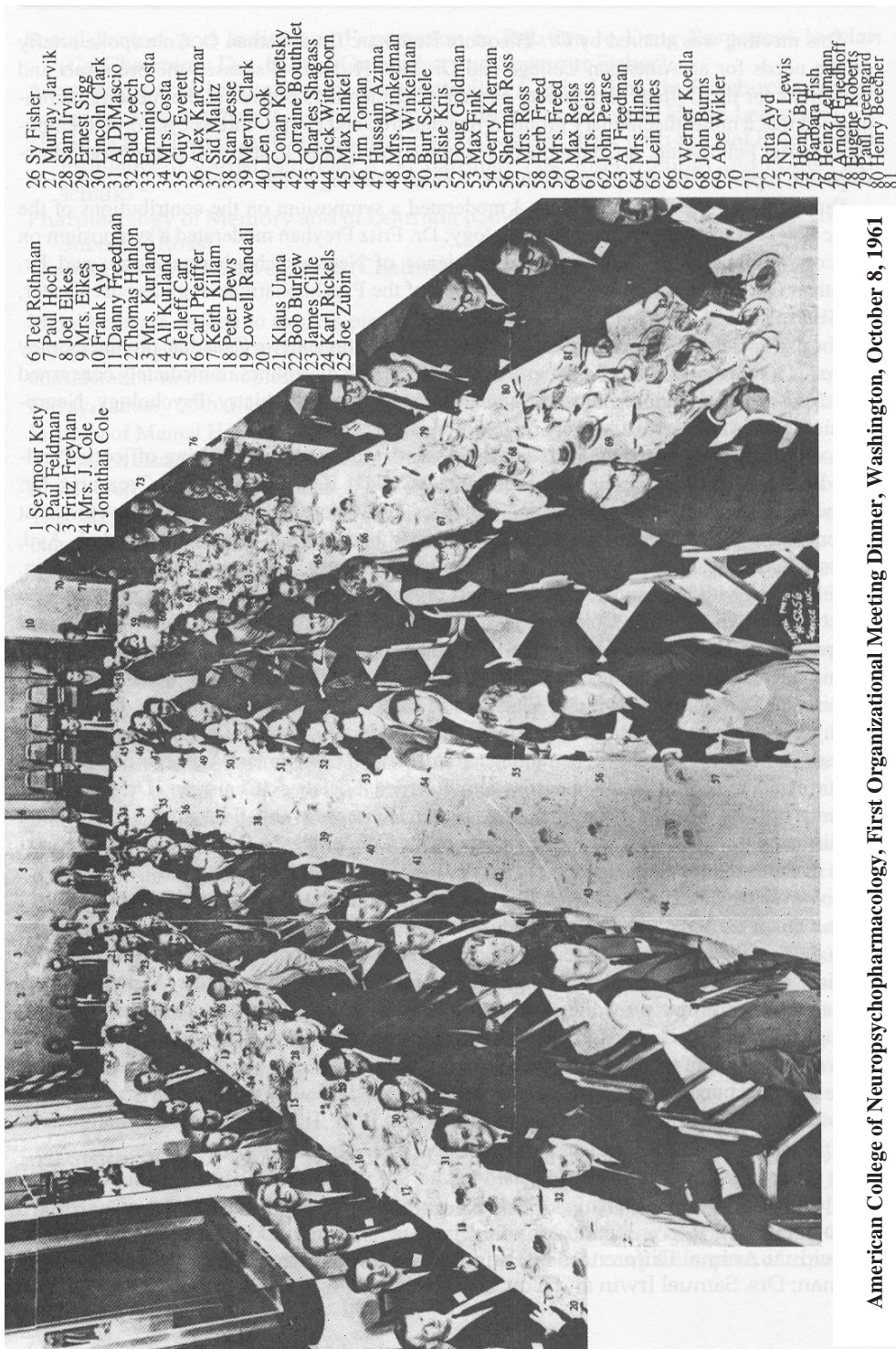
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from the *ACNP Bulletin* 1: 2-3, 1962

It is both timely and pleasant to recall, on the occasion of the first issue of the Bulletin, the events which led to the establishment of our young organization.

On November 12-13, 1960, a Conference for the Advancement of Neuropsychopharmacology was held at the Barbizon-Plaza Hotel, New York City, organized by the convening Secretary, Dr. Theodore Rothman, under the Chairmanship of Dr. Paul Hoch. The main purpose of the Conference was to stimulate critical discussion and suggest proposals for the advancement of Neuropsychopharmacology.

There were twenty participants, and above twenty guests present at this Conference. The program was introduced by Dr. Rothman. The present situation in Neuropsychopharmacology and Psychiatry was discussed by Dr. Paul Hoch and Dr. Heinz Lehmann. Proposals were made to improve the evaluation of the psychoactive agents, and the dissemination of accurate information to investigators. These discussions were led by Dr. Paul Feldman and Dr. Jonathan Cole. Dr. Bernard Brodie opened a session dedicated to an evaluation of the present state of neuropsychopharmacological research; his paper was discussed by Dr. Abram Hoffer. Dr. Eugene M. Chaffey and Dr. Joseph M. Tobin spoke on the need of collaborative multidisciplinary research. Recommendations were made by Conference participants, and were summarized by Dr. Arnold Scheibel and Dr. James T. Ferguson. The most important of these was a recommendation for the creation of a Committee to organize an American College of Neuropsychopharmacology. Dr. Theodore Rothman was elected Chairman of this Organizing Committee; other members were Dr. Frank J. Ayd, Dr. Bernard B. Brodie, Dr. Jonathan O. Cole, Dr. Paul Feldman and Dr. Paul H. Hoch.

Dr. Rothman and the Organizing Committee met numerous times during the following months and spent many hours investigating, inquiring, studying and readying plans for an organizational meeting of interested individuals drawn from Neuropsychopharmacology and its allied fields, with the set purpose of creating a permanent Society for the Advancement of Neuropsychopharmacology. A draft of a Constitution and By-Laws was formulated, and steps taken to form a non-profit, scientific research corporation in the State of Maryland, to be known as the American College of Neuropsychopharmacology. These preparations led ultimately to the First Organizational Meeting of the American College of Neuropsychopharmacology, which was held in Washington, D. C., on October 7-8, 1961.



- 1 Seymour Kety
- 2 Paul Feldman
- 3 Fritz Freyhan
- 4 Mrs. J. Cole
- 5 Jonathan Cole

- 6 Ted Rothman
- 7 Paul Hoch
- 8 Joel Elkes
- 9 Mrs. Elkes
- 10 Frank Ayd
- 11 Danny Freedman
- 12 Thomas Hanlon
- 13 Mrs. Kurland
- 14 All Kurland
- 15 Jelleff Carr
- 16 Carl Pfeiffer
- 17 Keith Killam
- 18 Peter Dewes
- 19 Lowell Randall
- 20
- 21 Klaus Unna
- 22 Bob Burlew
- 23 James Cille
- 24 Karl Rickels
- 25 Joe Zubin

- 26 Sy Fisher
- 27 Murray Jarvik
- 28 Sam Irvin
- 29 Ernest Sigg
- 30 Lincoln Clark
- 31 Al DiMascio
- 32 Bud Veech
- 33 Ermnio Costa
- 34 Mrs. Costa
- 35 Guy Everett
- 36 Alex Karczmar
- 37 Sid Maltz
- 38 Stan Lesse
- 39 Mervin Clark
- 40 Len Cook
- 41 Conan Kornetsky
- 42 Lorraine Bouthilet
- 43 Charles Shagass
- 44 Dick Wittenborn
- 45 Max Rinkel
- 46 Jim Toman
- 47 Hussain Azima
- 48 Mrs. Winkelman
- 49 Bill Winkelman
- 50 Burt Schiele
- 51 Elsie Kris
- 52 Doug Goldman
- 53 Max Fink
- 54 Gerry Klerman
- 56 Sherman Ross
- 57 Mrs. Ross
- 58 Herb Freed
- 59 Mrs. Freed
- 60 Max Reiss
- 61 Mrs. Reiss
- 62 John Pearse
- 63 Al Freedman
- 64 Mrs. Hines
- 65 Lein Hines
- 66
- 67 Werner Koella
- 68 John Burns
- 69 Abe Wikler
- 70
- 71
- 72 Rita Ayd
- 73 N.D.C. Lewis
- 74 Henry Brill
- 75 Barbara Fish
- 76 Heinz Lehmann
- 77 Arnold Friedhoff
- 78 Eugene Roberts
- 79 Paul Greengard
- 80 Henry Beecher
- 81

American College of Neuropsychopharmacology, First Organizational Meeting Dinner, Washington, October 8, 1961

This meeting was chaired by Dr. Theodore Rothman. Dr. Jonathan O. Cole spoke briefly on the needs for an American College and Dr. Paul H. Hoch discussed the proposals and objectives for the College. The ninety participating members present at the meeting recommended that a multi-disciplinary group of one hundred and twenty-three be accorded temporary Charter Fellowship. A Credentials Committee was formed to study all temporary fellowships and report to the members at the next Annual Meeting of the ACNP.

During the course of the meeting, I moderated a symposium on the contributions of the Basic Sciences to Neuropsychopharmacology; Dr. Fritz Freyhan moderated a symposium on the contributions of the clinician to the Science of Neuropsychopharmacology; and Dr. Jonathan O. Cole spoke on the current program of the Psychopharmacology Service Center, NIMH.

The participating members represented twenty-two states and two Canadian provinces; they approved a Constitution and By-Laws for the College. All disciplines immediately concerned with Neuropsychopharmacology, including Pharmacology, Psychiatry, Psychology, Neurophysiology and Biochemistry, were represented at the meeting.

It was during this meeting, also, that the Assembly elected the following officers; President-Elect, Dr. Paul H. Hoch; Vice-President, Dr. Klaus R. Unna; Secretary-Treasurer, Dr. Theodore Rothman; Assistant Secretary-Treasurer, Dr. Milton Greenblatt; and did me the great honor of electing me First President. Council members elected were: Drs. Frank J. Ayd, Bernard B. Brodic, Jonathan O. Cole, Heinz E. Lehman, James E. P. Toman, and Joseph Zubin.

In keeping with its mandate from this first organizational meeting, Council proceeded to structure the work of the College by way of its various committees. These committees comprised the Nominating Committee (Chairman, Dr. M. Rinkel); Credentials Committee (Chairman, Dr. Fritz A. Freyhan); Program and Scientific Communications Committee (Chairman, Dr. Jonathan O. Cole); Finance and Budget Committee (Chairman, Dr. Paul H. Hoch); Publications Committee (Chairman, Dr. Theodore Rothman). Other committees concerned themselves with matters pertaining to Liaison with Government Agencies and Industry (Chairman, Dr. Henry Brill); Liaison with Learned Societies (Chairman, Dr. Ralph W. Gerard); Ethical Matters (Chairman, Dr. Nolan D. Lewis); and Education and Training (Chairman, Dr. Klaus R. Unna). The reports of the Committees will be included in the next issue of the Bulletin.

However, as with all committees, their work can but reflect the work of the membership at large. Ours is an active association; and it was indeed warming to me to receive, during the early days of the College, such ready response to my suggestion that we form Study Groups within the College. The small size of our College is our ally in this venture. Members know one another well, thus providing a ready opportunity to clarify some controversial issues through frank debate in small groups. It was suggested that Study Groups address themselves to an examination of topics which were either vague or controversial, or of special relevance to the practical pursuit of some areas of investigation; and that they do so over a period of time to ensure a definitive summary of the state of a given field. The topics chosen initially were:

Individual Variation in the Metabolism of Psychoactive Drugs (Co-Chairman: Drs. B.B. Brodic and Albert Kurland)

Analysis of the Effect of Drugs on the Electrical Activity of the Brain (Co-Chairman: Drs. James E.P. Toman and Max Fink)

Individual Animal Differences in Drug Responses; Determining Factors (Co-Chairman: Drs. Samuel Irwin and Conan Kornetsky)

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- Social Factors and Individual Expectation in Relation to Drug Responses in Man (Co-Chairman: Drs. Milton Greenblatt and Seymour Fisher)
- Advantages and Limitations of the Controlled Clinical Trial in Psychopharmacological Investigation (Co-Chairman: Drs. Jonathan Cole and Heinz Lehmann)
- The Effects of Drugs on Communication Processes in Man with Special Reference to Problems of Verbal Behavior (Co-Chairman: Drs. Joseph Zubin and Louis Gottschalk)
- Pharmacology of Memory and of Learning (Co-Chairman: Drs. Murray E. Jarvik and Sherman Ross)
- Toxicity of Psychoactive Drugs (Chairman: Dr. Klaus Unna)

Members were invited to express preferences for one or another of the Study Groups. The groups having been once constituted, met at the call of their co-chairman and gave lively consideration to their topics for a whole day at the First Annual Meeting of the College, on Friday, January 25th. It is anticipated that, with the help of a generous grant from the National Institute of Mental Health, this work will now continue for the next two years.

Council also considered a further suggestion; namely, the institution, at an appropriate time in the future, of practical Courses and Workshops in various aspects of Psychopharmacology. This suggestion stemmed from the conviction that the Science of Psychopharmacology can only be as good as its methods; and that it was appropriate for the College to face the responsibility of providing training opportunities in the various techniques currently used in the field, and to make available to members (and possibly, to others) the reservoir of skills comprised within the College. It is quite conceivable that such Practice Training Workshops may lead to the development of training manuals in various areas, resulting, over the years, in a series of authoritative, up-to-date Teaching Texts in Research Methods in Psychopharmacology. These could range from Neurobiological to Behavioral Techniques and comprise both Experimental and Clinical aspects.

In looking back over its short history from that early meeting at the Barbizon-Plaza to the present day, it is hard not to be encouraged by the vigor and variety of programs developing within our small association. It is not uncommon for anyone of us to be told that Psychopharmacology is not a science, and that it would do well to emulate the precision of older and more established disciplines. Such statements betray a lack of understanding for the special demands made by Psychopharmacology upon the fields which compound it. For I know of no other branch of science which like a good plough on a spring day, has tilled as many areas as Neurobiology. To have, in a mere decade, questioned the concept of synaptic transmission in the central nervous system; to have emphasized compartmentalisation and regionalization of chemical process in the unit cell, and in the brain; to have focussed on the interaction of hormone and chemical process within the brain; to have given us tools for the study of the chemical basis of learning and temporary connection formation; to have emphasized the dependence of pharmacological response on its situational and social setting; to have compelled a hard look at the semantics of psychiatric diagnosis, description and communication; to have resuscitated that oldest of old remedies, the placebo response, for careful scrutiny; to have provided potential methods for the study of language in relation to the functional state of the brain; and to have encouraged the Biochemist, Physiologist, Psychologist, Clinician and the Mathematician and Communication Engineer to join forces at bench level, is no mean achievement for a young science. That a chemical text should carry the imprint of experience,

and partake in its growth, in no way invalidates study of the symbols, and the rules among symbols, which keep us going, changing, evolving, and human.

Thus, though moving cautiously from set habit to positive scepticism, Psychopharmacology is still protesting; yet, in so doing it is, for the first time, compelling the physical and chemical sciences to look behavior in the face, and thus enriching both. If there be discomfiture in this encounter, it is hardly surprising; for it is in this discomfiture that there may well lie the germ of a new science.



## **6 AN OVERVIEW OF SELECTED WRITINGS OF JOEL ELKES**

Selected Writings of Joel Elkes was first published by Animula (for CINP) in 2001. A second edition of the book was prepared by Gregers Wegener during Robert H. Belmaker's presidency and published by CINP in 2010. The book was edited by Thomas A. Ban with introductions by Floyd E. Bloom and Philip B. Bradley. The content of Selected Writings is not restricted to a collection of Joel Elkes' papers in neuropsychopharmacology; it also includes his contributions to other areas in the behavioral sciences and some of his personal reflections.

The material presented in Selected Writings is organized into 12 parts. Part One ("Overviews") includes five papers from which in three the program on Drugs and the Mind, Elkes developed in the Department of Pharmacology at the University of Birmingham in England between 1947 and 1951, is presented, and two are addresses he delivered at meetings of the American College of Neuropsychopharmacology, an organization he was the founding president, one in 1962, and the other in 1992. Elkes' program, Drugs and the Mind received recognition by the University by the establishment of the first independent Department of Experimental Psychiatry in the world under his leadership, in 1951.

In Part Two ("Early papers: Physical chemistry and X-ray diffraction") Elkes presents his findings with J. B. Finean, his first PhD student, a crystallographer, on lipid/protein interactions in biological membranes, in three papers. They also describe X-ray diffraction studies of living myelin, using an irrigated frog sciatic nerve preparation.

Part Three ("Electrophysiological studies in Birmingham and an early clinical trial") includes five papers in which Elkes' findings with Philip Bradley on the effect of some drugs on the electrical activity of the brain are presented, and the results of the first blind-controlled trial of chlorpromazine in overactive psychiatric patients, he carried out in collaboration with his late first wife, Charmian Elkes, are discussed. It also includes papers in which some of Elkes' ideas on the use of pharmacology in the study of mental organization is outlined, and in which he introduces some, at the time novel concepts on the existence of distinct families of neuroregulatory compounds ("neurotransmitters"), related to chemically distinct neurone populations, carrying specific receptors, in the brain..

In Part Four (“Reviews”) Elkes examines in three papers the four footings of a science of psychopharmacology: functional neuroanatomy, electrophysiology, animal behavior and the human experiment and clinical trial. He emphasizes the need for a deeper understanding of regional process in the brain as it sub-serves its integrative function.

Part Five (“Schizophrenic disorder as a disorder of chemically mediated information processing in the brain”) includes only one paper in which Elkes argues that schizophrenic disorder represents a decompensation, or failure of a fundamental organizing process in the brain concerned with the processing of information at perceptual, affective and cognitive levels.

Part Six [“A perspective (1978)”] includes also only one paper. It is written as a letter to an aspiring young colleague and it deals with chemical mapping and neurochemical specificities of the brain; the promise and drawback of metabolic loading studies; the promise of discriminate use of drugs in a taxonomy of mental disorders; the chemical correlates of coping and well being; and the possible extension of physiological boundaries. The letter ends with Elkes’ plea for new mathematical languages for the description of the nonlinear stochastic phenomena, he believes are the business of much of future psychopharmacology.

Part Seven (“Humanizing the education of physicians. The behavioral sciences` in the service of medicine”) includes four papers from which in the first three Elkes outlines his ideas how modern psychiatry could relate and translate modern biology to the behavioral sciences and the behavioral sciences to the body of clinical medicine. He emphasizes the crucial role of trans-disciplinary communication and the need for a common language through joint work. He put his ideas expressed in these papers in operation in an MD-PhD program he organized at Johns Hopkins University in collaboration with three other departmental chairmen between 1973 and 1975. In the fourth paper he elaborates on the need for enhancing the awareness of medical student on their own health needs, and honing their coping skills early in their career. He also put these ideas in operation with the help of Leah Dickenstein at the time Dean of Students, at the University of Louisville, Kentucky, in the “Louisville Experiment” in John Schwab’s Department of psychiatry at the University.

In Part Eight (“Five lectures”) the full text of five invited lectures are presented. In his two “Salmon Lectures,” he deals with “Chemistry, Awareness and Imagination”; in his ‘Harvey

Lecture,” Elkes discusses “Subjective and objective observation in psychiatry”; in his Jacob Bronowski Memorial Lecture,” he talks “On the neurosciences, awareness, choice and the good day”; and in his “Distinguished Psychiatrist Lecture” (American Psychiatric Association”), he talks “On psychobiology and communication: psychiatry and the future of medicine”.

Part Nine (“The Community as an agent of proactive health care and health enhancement”) is centered around the Columbia project, a social experiment in which a city, Columbia in Howard County, Maryland, was created, with the help of the Rouse Company, that offered unprecedented opportunities for providing cost-effective medical services, including mental health services with emphasis on prevention and prompt mental health intervention. From the two papers included in this part, one is Elkes’ letter to James Rouse, the visionary developer of the city, in which he propose the creation of a Center for the Study of Human Development in the city as a joint venture between his Department of Psychiatry at Johns Hopkins University and the Columbia Association. The other paper in this part is the transcript of an interview with Joel Elkes and his late first wife, Charmian, the first chief of psychiatry at the Columbia Clinic, about the Columbia Plan and the Columbia Clinic.

In the two papers of Part Ten (Holocaust and Israel) Elkes provides a context of his art and his work in Israel. Elkes received his high school education in Kovno, Lithuania. His father Dr. Elchanan Elkes, a prominent Lithanian physician and elected head of the Kovno Ghetto after the German occupation in 1941, died in Dachau in October 1943. Elkes wrote a memoir on his father that he delivered at the holocaust commemorative ceremony at the Kentucky Center of Art in Louisville on April 17, 1985. One of the two papers of Part Ten is the text of his memorial lecture. The other paper is his Introductory Remarks at the 25<sup>th</sup> Anniversary Symposium of the National Institute of Psychobiology in Israel in Memory of Charles E. Smith, whose generous support helped him to found the Israel Center of Psychobiology.

Part Eleven (Two Friends) includes three papers. One is a letter to Jonas Salk on his 80<sup>th</sup> birthday. Salk was a long time friend of Elkes; they organized together the first Symposium on the Neurosciences at the Salk Institute which later led to the formation of the Program on Neurosciences at the Institute. The second is a review of Norman Cousins’s book *The Healing Heart: Antidotes to Panic and Helplessness*. The third, is a tribute to Cousins, who was supportive of Elkes’ program on Health Awareness of Medical Students in Louisville, and also of the work

of Elkes' late second wife, Josephine Rhodes, on Professional Peer Group Counseling in Rheumatoid Arthritis.

In Part Twelve (On Art and Healing), the last part of the book, Elkes describes the Program in the Arts and Medicine he developed in the Department of Psychiatry, at the University of Louisville. His aim was to introduce the "soft" Arts to the "hard" Sciences and bring about a meeting of two cultures, the culture of the arts and of the Medical Sciences in a School of Medicine, in his overall effort to humanize the education of physicians.

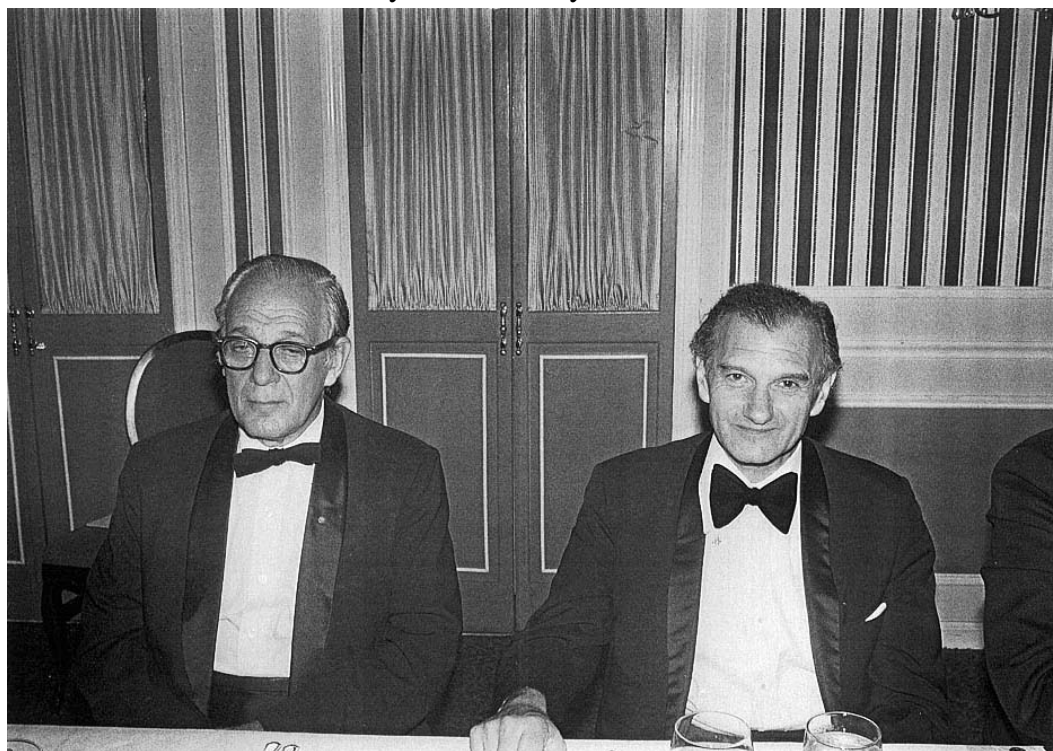
Selected Writings is dedicated to the "women of his life": Sally Ruth, his third wife, Sara, his sister, Anna, his daughter, and Laura, his granddaughter. It concludes with Elkes' art and is supplemented with photos of a selection of his paintings.

## 7 PHOTO ARCHIVES

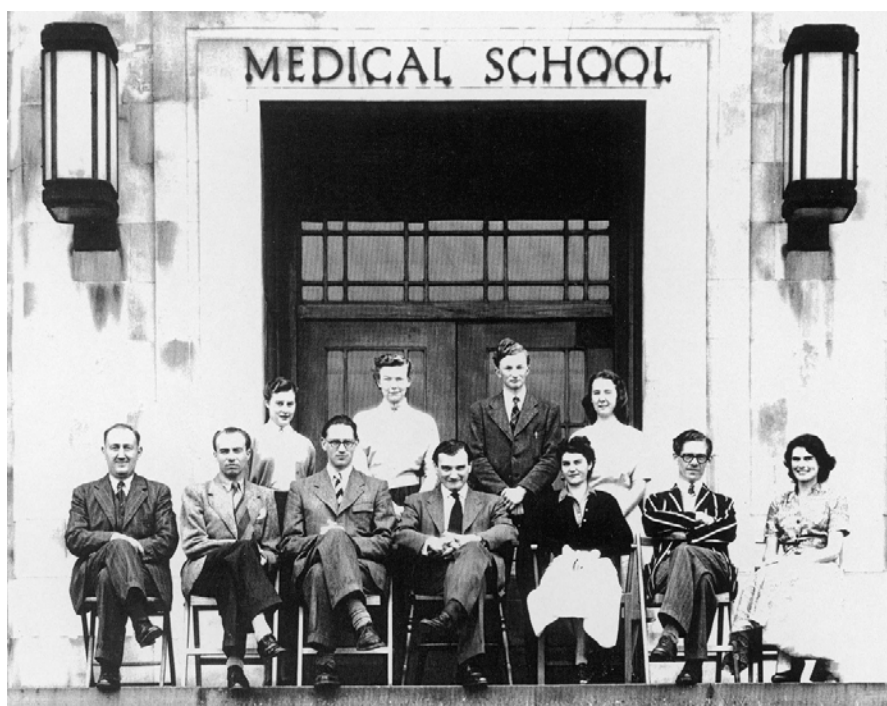
It includes ten photos of Joel Elkes with his peers adopted from CINP's International Photo Archives in Neuropsychopharmacology, presented in chronological order with the place and approximate time photo was taken identified if available.

The names of people on each photo are listed from left to right. The Arabic numeral beside the name(s) indicates the position of the person on the photo.

### 7.1 Seymour S. Kety and Joel Elkes



7.2 Philip B. Bradley(3), Joel Elkes (4), Charmian Elkes (5), Department of Experimental Psychiatry, University of Birmingham, Birmingham, England, Mid-1950s



7.3 Joel Elkes (2), P.B. Schneider (3), M. Kramer (4), WHO Study Group, Geneva, Switzerland, 1957



7.4 D. Ewen Cameron (2), Heinz E. Lehmann (3), Paul Hoch (4), Joel Elkes (5), 112<sup>th</sup>  
Annual meeting of the APA, Philadelphia, Pennsylvania, USA, 1959



7.5 Fritz Freyhan (2), Joel Elkes (3), Clinical Pharmacology Research Center, St.  
Elizabeths' Hospital, The William A. White Building Washington, DC, USA, 1957-  
1963



7.6 Robert Maxwell (3), Joel Elkes (5), Seymour Kety (6), Clinical Pharmacology Research Center, St. Elizabeths' Hospital, The William A. White Building, Washington, DC, USA, 1957-1963



7.7 Floyd Bloom (1), Joel Elkes (2), Fritz Freyhan (3), Clinical Pharmacology Research Center, St. Elizabeths' Hospital, The William A. White Building, Washington, DC, USA, 1957-1963





7.8 Floyd Bloom (2), Joel Elkes (3), Clinical Pharmacology Research Center, St. Elizabeths' Hospital, The William A. White Building. Washington, DC, USA, 1957-1963



7.9 Jorge Perez-Cruet, (3), G. Marazzi (4), Joel Elkes (5) Thomas Ban (6), Charles Shagass (7), 5<sup>th</sup> CINP Congress, Washington, DC, USA, 1966



7.10 Claude de Montigny, (1), Joel Elkes (2), Sam Wong (3), 21<sup>st</sup> CINP Congress, Glasgow, Scotland, 1998



## **8 THE ARTIST**

Joel Elkes dabbled in painting during his days in high school. He resumed it during World War II and his early days in Birmingham. Since the late 1980s Joel has dedicated time regularly to his art.

In closing, on the painting below you can see Joel in his studio circa 1965, followed by a selection of photos of his paintings.





The Rocks at Joggins (1990)



Patterns in Rocks (1989)



Pool and Rocks (1989)



A Conversation (1988)





Shore Colors, Afternoon (1990)



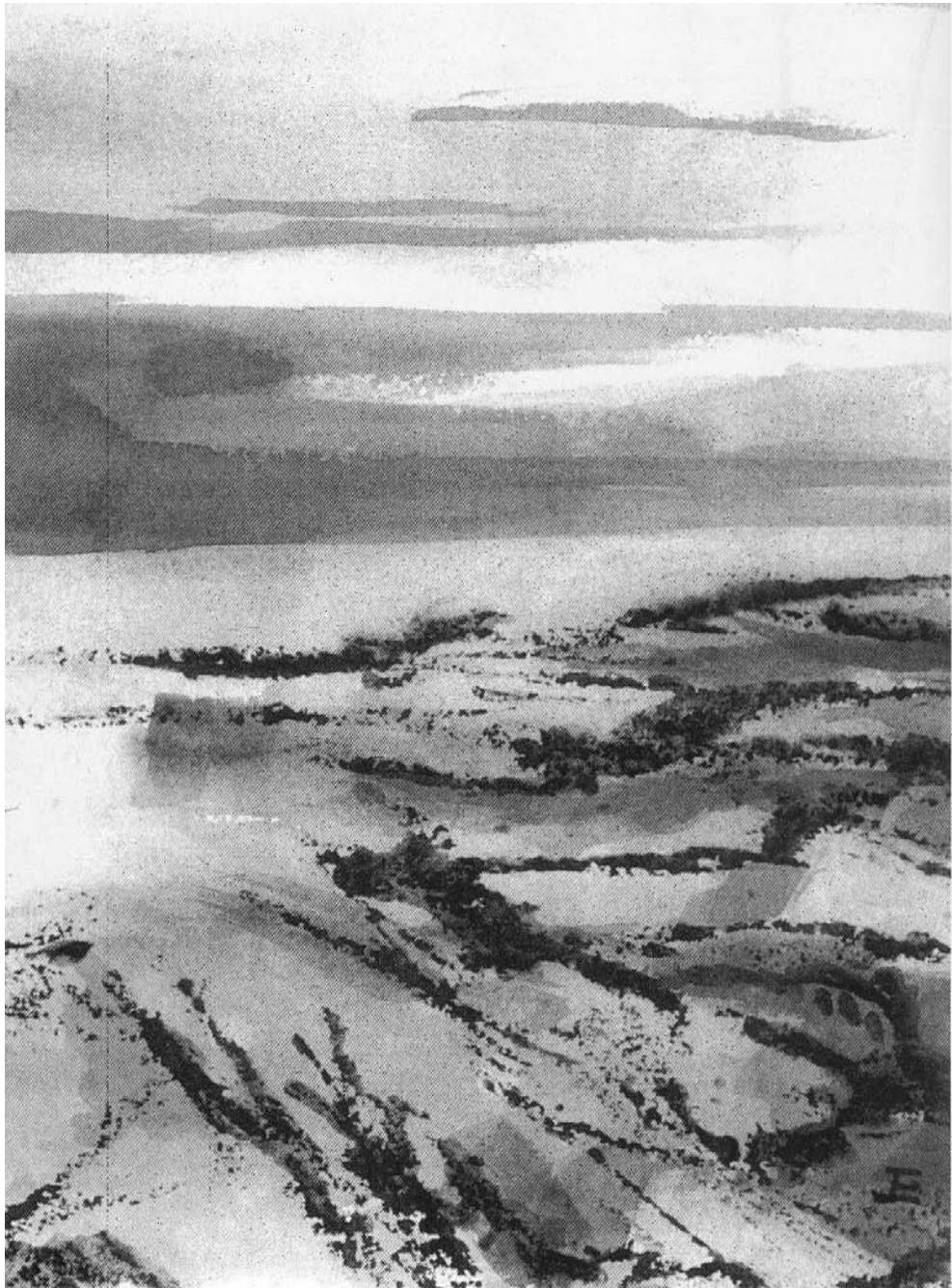
On my Walk (1990)



Tree Form (1992)



Pool and rocks II (1989)



After the rain (1991)



Forms by Shore (1990)



Dusk: Point Prim, P.E.I. (1990)



Rocks, Afternoon (1991)





Afternoon Light (1988)



Play of Light, Afternoon (1992)



The Light and the Dark (1992)