An Oral History Of Neuropsychopharmacology

The First Fifty Years
Peer Interviews

SERIES EDITED BY: Thomas A. Ban

Volume Nine: UPDATE
EDITED BY: Barry Blackwell

American College of Neuropsychopharmacology
AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY
THE FIRST FIFTY YEARS
Peer Interviews

Volume Nine: Update
VOLUME 9

Barry Blackwell

UPDATE

Preface
Thomas A. Ban
Dedicated to the Memory of Nathan S. Kline, President ACNP, 1967
In the first eight volumes of this ten-volume series, interviewees reflect on their contributions to the development of neuropsychopharmacology. Volume Nine (Update) differs from all prior volumes in that it includes a second interview that complements and updates the information in the first interviews. These second interviews were not planned. They were done on request of the interviewees or others, most often for adding to the information covered in the first interviews.

In Volume Nine, interviewees contributed to diverse areas of research in neuropsychopharmacology. Hence, in the same way as in Volume Eight (Diverse Topics), the information in the transcripts provides the prime material for an overview of the changes which have taken place in neuropsychopharmacology since the 1950s.

During its first fifty years neuropsychopharmacology was a rapidly moving field. In the 1960s behavioral pharmacology (see, Volume 1) was replaced by neuropharmacology (see, Volume 3) in the screening and preclinical development of psychotropic drugs. In the 1970s, research in neuropharmacology was extended from cerebral monoamines to neurotransmitter modulators, peptides and prostaglandins; interest shifted from pre-synaptic to post-synaptic mechanisms; and studies of neurotransmitter biochemistry were supplemented with studies on receptor affinities. In the 1980s electrophysiological studies were complemented by studies of brain metabolism with the employment of brain imaging (see, Volume 2) and research studies on the effect of drugs on “wiring transmission” by studies on the effect of drugs on “volume transmission.” (See, Fuxe Volume 3.)

In the 1990s, with the sequencing of the human genome from 1989 to 2004, a molecular genetic (pharmacogenetic) approach emerged and in a decade replaced the “traditional” biochemical approach in the study of the biology of mental illness. By the dawn of the 21st century, the neurotransmitter era, the first epoch in the history of neuropsychopharmacology was succeeded by a molecular genetic era, opening up a new perspective for developing psychotropic drugs.

The subject matter of this volume is the charting of this rapid transformation of the field in the thoughts, writings and research of the interviewees.

* Volume One: Starting Up (behavioural pharmacology); Volume Two: Neurophysiology (electrophysiology & brain imaging); Volume Three: Neuropharmacology; Volume Four: Psychopharmacology; Volume Five: Neuropsychopharmacology; Volume Six: Addiction; Volume Seven: Special Areas (child psychiatry, geriatric psychiatry, diagnosis and pharmacokinetics); Volume Eight: Diverse Topics.
As in all prior volumes in this series, the first part of the Preface provides orientation points for placing interviewees’ contributions into a historical context and the last part reviews personal contributions. Although there are some overlaps, the vignettes in this volume on interviewees’ contributions differ from the vignettes in prior volumes. In Volume Nine the vignettes are based primarily on what interviewees themselves consider their most important contributions to neuropsychopharmacology, whereas in the other volumes they are based on editor’s judgment about interviewees’ contributions to the particular area of research covered in the volume. Another difference is that in Volume Nine, special attention is paid to early and most recent contributions.

Pharmacogenetics

The term “pharmacogenetics”, was coined by Friedrich Vogel in 1959, about six years after James Watson and Francis Crick proposed (in 1953) the “double helix” as the structure of the human DNA (deoxyribonucleic acid.)

The roots of pharmacogenetics are in Archibald Garrod’s recognition in the first decade of the 20th century that genetic factors “direct” the chemical transformation (metabolism) of drugs in the body. The first systematic account on pharmacogenetics was published in 1962 by Werner Kalow.

Pharmacogenetics studies inter-individual differences in response to drugs. The objective is to identify and characterize genetic factors that underlie differential responsiveness to drugs between groups and between individuals within a group. Accordingly, one area of pharmacogenetic research is focused on the responses of patients with different psychiatric diagnoses to the pharmacodynamic properties of the same drug, whereas another area of research is focused on genetically-based pharmacokinetic differences between members of the same diagnostic group in responding to the same drug.

The genetics of pharmacokinetic differences entered psychiatric pharmacotherapy in 1960 with Evans and associates’ recognition that the rate of acetylation of isoniazid, is under genetic control. In 1964 they reported that patients who metabolize phenelzine* at a relatively lower rate, as measured by the ratio of acetylated to free sulfapyridine in urine after sulfamethazine administration, developed more side effects to the drug. These findings were complemented by the work of Johnstone, who reported in 1966 that “slow acetylators” respond more favorably to the drug. Nevertheless, the relationship between acetylator status and response to treatment has remained tenuous; Robinson and associates found no difference between

* Phenelzine is a monoamine oxidase inhibitor antidepressant that shares with isoniazid and iproniazid a hydrazine moiety.
slow and fast acetylators in therapeutic response, side effects and platelet monoamine oxidase inhibition in patients treated with phenelzine. (See, Robinson, Volume 5.)

The genetics of pharmacodynamic differences entered psychiatry in the 1990s in molecular genetic studies of schizophrenia and manic-depressive illness. On the basis of the mode of action of drugs with demonstrated therapeutic efficacy, various genes which encode transporters (e.g., the serotonin transporter, the dopamine transporter), receptors (e.g., the serotonin-5HT<sub>2A</sub> receptor, the dopamine-D<sub>2</sub> and D<sub>3</sub> receptors), and enzymes (e.g., monoamine oxidase, dopamine-β-hydroxylase, catechol-methyl-transferase), have been implicated in the pathophysiology of these diseases. Genetic "association studies" however, have failed to detect consistent differences in mutations (polymorphism), in the implicated genes, between normal volunteers and patients with either of these diseases. (See, Kety, Volume 2, and Wender, Volume 7.)

**Genetics and Neuropsychopharmacology**

The observation that mental illness runs in families has been documented since the mid-18<sup>th</sup> century; the first genetic theory of mental illness was formulated by Morel in the mid-1850s. It was based on the assumption of "degeneration", the notion that mental disease is the result of an "innate biological defect" that becomes manifest in increasingly severe mental syndromes in "lineal descents." Morel's degeneration theory was replaced by Moebius' "endogeny theory", in the 1890s which implicated a "constitutionally determined predisposition" for developing mental illness.

The heredity of mental illness received substantial support in epidemiologic genetic studies. The risk of developing schizophrenia for relatives of patients with schizophrenia and manic-depressive illness was found to be consistently higher than in the general population; and the risk of developing the respective illness in both diagnostic groups was found to be higher for first, than for second degree relatives. Furthermore, children of schizophrenic biological parents adopted into the families of non-schizophrenic foster parents were found to develop schizophrenia at a much higher rate than adopted away children of normal parents, and mental illness was found to occur also at a much higher rate in the biological than in the adoptive families of adopted schizophrenic and manic-depressive children. (See, Kety, Volume 2, and Wender, Volume 7.)

In spite of evidence, that mental illness runs in families, molecular genetic studies using "linkage analysis", "positional cloning", and "genome scanning", yielded inconsistent findings. Susceptibility loci for schizophrenia
and manic-depressive illness were reported on various, chromosomes,* the findings in one group of patients, however, could not be replicated in others.30 Failure to replicate findings in a similar diagnostic population from one study to the next indicates genetic heterogeneity within the diagnostic groups. Thus, the heterogeneity within diagnoses interfered with molecular genetic research in mental illness.31

The inconsistent findings in molecular genetic research lead to growing dissatisfaction with consensus-based classifications.32 The unhappiness was such that in 1999, Steven Hyman, at the time the Director of NIMH in the United States, pointed out that “it would be foolish to think” that diagnostic criteria in classifications like the DSM-IV would “select anything that maps into the genome”.33 It was also recognized that without a re-evaluation of diagnostic concepts in psychiatry, it would be futile to employ either a pharmacogenetic or a pharmacogenomic approach,34 in psychotropic drug development.35

The problem created by the genetic, pharmacological and psychopathological heterogeneity within diagnoses was compounded by the vanishing from view by the end of the 20th century of the two disciplines of psychiatry, psychopathology and psychiatric nosology that dealt with the delineation and classification of psychiatric diseases. Since both disciplines may offer leads for the identification of pharmacologically more homogeneous psychiatric populations than identified in consensus-based classifications, a subject matter central in the research of several interviewees in this volume, in the following two sections some of the basic tenets of psychopathology and psychiatric nosology are briefly reviewed.

**Psychopathology**

Psychopathology studies the symptoms and signs of psychiatric disease. The term, psychopathology, first appeared in 1845, in Ernst Feuchtersleben’s textbook on “psychic diseases”.36 Subsequently, it was used only sporadically, as a generic term for psychiatry in the rest of the 19th century.37,38,39,40 **

Development of modern psychopathology began in the early 20th century with Karl Jaspers’ recognition that patients with different psychiatric disease perceive the same experience differently. His adoption of the Aristotelian distinction between “form” and “content” in the analysis of psychiatric symptoms

---

* Susceptibility loci for were reported for schizophrenia on chromosomes 1q, 3p, 5q, 5p, 8q, 9p, 10q, 12q, 13p, 14p, 15q, 20p and 22q; and for manic-depressive illness on chromosomes 4p, 5p, 6p, 18q, 20p, 21q and 22q.

**During the 19th century the terminology of psychopathology steadily grew: Equirol in the 1830s divided false perceptions into “illusions” and “hallucinations”; Griesinger in the 1840s distinguished “pale” or “pseudo-hallucinations” from “true” or “real” hallucinations”; Wernicke in the 1880s separated “dysmnesia” from “dementia”.

---
led in 1910, to the separation of “psychiatric disease” from “abnormal personality development”.

In 1913, by distinguishing between “phenomenology” and “performance psychology” in his *General Psychopathology*, Jaspers opened up a new perspective for studying the pathology of a group of diseases referred to at the time as “functional” or “endogenous” psychoses.

In phenomenological psychopathology, the distinction between “form” and “content” provides a means for the detection and differentiation of the pathological experiences encountered by patients. In a phenomenological analysis it is not the subject matter, the “content” (e.g., a “somatic hypochondriacal complaint”), but the “form” in which this content is experienced by the patient, e.g., “bodily hallucinations”, “obsessive ideas”, “hypochondriacal delusions”, that is relevant to patient’s illness and psychiatric diagnosis.

From 1918 to 1933 a group of psychiatrists in Kurt Wilmann’s department of psychiatry at Heidelberg University embarked on “phenomenological analysis” of the psychopathological symptom displayed in psychiatric patients’. Their research yielded a set of symptoms that reflect the pathologies in the processing of signals in the brain from “symbolization” to “psychomotility”. It also provided fine distinctions between manifestations, such as the difference between “dysphoria” and “dysthymia”, “psychomotor retardation” and “psychomotor inhibition”, etc. By linking the pathologies in the processing of signals to psychiatric diagnoses, e.g., “tangential thinking” to the schizophrenias, “circumstantial thinking” to the dementias, “rumination” to the depressions, the Heidelberg school, set the foundation for a language of psychiatry that reflects the ongoing functional pathology in the brain.

The notion that different psychopathologic symptoms reflect different pathologies in the processing of experience in the brain was in keeping with Ramon y Cajal’s contributions in the late 19th and early 20th century. His findings that neural circuits in the brain consist of sensory, motor, and inter-neurons, and his demonstration of the “connection specificity of neurons”, provided the neural underpinning of “structural psychopathology”, spearheaded by Gyula Nyirö in the mid-20th century.

In structural psychopathology, psychopathological symptoms are organized as in Carl Wernicke’s classification into three psychic structures, based on the three phases of reflex mechanism: (1) afferent – cognitive, (2) central – affective and (3) efferent – adaptive. Each structure has several levels* and each level is connected with each level within and across structures. For the

* In structural psychopathology the five levels of the afferent – cognitive structure are: diffuse sensation, differentiated perception, image formation, concrete ideation and abstract ideation; the four levels of the central – affective structure are: undifferentiated primitive signal, sensorial and vital emotions, intellectual emotions and ethical, moral and social emotions; and the six levels of the efferent – adaptive structure are: autonomic (vegetative) movements and simple elementary reflexes, in-coordinated movements, emotional and instinctual stereotype, echo movements, voluntary coordinated movements, and automatisms.
structural psychopathologist, psychopathological symptoms are abnormalities in these connections. Operating within a Pavlovian frame of reference (see, Preface, Volume 2, and Postscript, Volume 10), Nyiro opened the path for the study of psychopathological symptoms with conditioned reflex methods.\textsuperscript{52}

**Nosology**

Psychiatric nosology deals with the methodology of synthesizing psychopathological symptoms into diseases and in classifying the diseases synthesized.\textsuperscript{53} The term “nosology”, first appeared in 1743 in Robert James’ Medical Dictionary.\textsuperscript{54} Development of “nosology”, as a discipline was triggered well over 100 years later, in the mid-18\textsuperscript{th} century, by François Boissier de Sauvage’s postulation that a disease should be defined by “the enumeration of symptoms that suffice to recognize it and distinguish it from other diseases”. One of the essential nosologic premises is that a classification should “allow the attribution of each patient to one and only one class.”\textsuperscript{55}

The first, nosologic organizing principle of “madness,” was introduced by William Cullen.\textsuperscript{56} His division of the “vesaniæ”, which included all the different forms of madness, on the basis of “totality,” into “mania,” or “universal madness,” and melancholia,” or “partial madness,” dominated classifications in psychiatry during the 19\textsuperscript{th} century.\textsuperscript{57,58*}

Adoption of Thomas Sydenham’s conceptualization of disease\textsuperscript{59} as a “process” with a “natural history of its own” that “runs a regular and predictable course”, led to the identification and classification of psychiatric diseases on the basis of their “temporal characteristics”, including “onset” (sudden or insidious), “course” (episodic or continuous) and “outcome” (recovery or defect). It was Jean Pierre Falret first in 1854 to identify a psychiatric disease, “folie circulaire”,\textsuperscript{60} on the basis of its “temporal” characteristics. Karl Kahlbaum in 1863 also proposed temporal course as a principle of classification without much resonance. (See, Preface, Volume 7.) So, it was only with Emil Kraepelin’s disease-oriented classification, in the 6\textsuperscript{th} edition of his textbook,\textsuperscript{61} published in 1899, that “temporal characteristics” firmly entered psychiatry as a classifying principle of mental disease. Kraepelin’s division (“dichotomy”) of the “endogenous psychoses” into “manic depressive insanity”, a disease that follows an episodic course with full remission between episodes, and “dementia

---

* The prototype of “partial insanity” was Lasègue’s diagnostic concept of “persecutory delusional psychosis”, the predecessor of Kahlbaum’s diagnostic concept of “paranoia”. In the prototype, “partial” means that the personality of patients remains preserved. A variation of “partial insanity” is “abortive insanity”, used in reference to Westphal’s diagnostic concept of “obsessive states”. In this context, “abortive” indicates that the “insight” of the patients about the pathological nature of their persistent and uncontrollable intrusion of thoughts, and urges to carry out actions, remains preserved. (See, Preface, Volume 7).
praecox”, a disease that follows a continuous deteriorating course, led to a re-evaluation of psychiatric diagnoses and classifications. In the course of this re-evaluation, diseases were divided into three groups. One of these groups, that includes diseases characterized by episodic course with full remission between episodes, becomes manifest in the form of “attacks” that last from minutes to hours (e.g., Martin Roth’s “phobic-anxiety-depersonalization syndrome”62), or in the form of “phases” that last from days to years (e.g., Edna Neele’s “phasic psychoses”63). Another group that includes diseases characterized by recurring episodes without full remission between episodes, becomes manifest in the form of “thrusts” or “shifts” (e.g., Eugen Bleuler’s “schizophrenias”64). The third group, that includes diseases characterized by continuous course, becomes manifest in the form of highly differentiated “end states” (e.g., Karl Leonhard’s “systematic schizophrenias”65), or in the form de-differentiated “dementia” (e.g., Alzheimer’s disease66).

Kraepelin’s classification was re-evaluated by Karl Kleist67,68 and Karl Leonhard69 between the 1920s and ‘50s. Adding “polarity” to “totatlity” and “temporality” in classifying psychiatric disease, Leonhard separates within the “endogenous psychoses” “bipolar,” multiform diseases, such as “manic-depressive illness”, from “unipolar”, monomorph diseases, such as the “systematic schizophrenias”, and unipolar “pure mania” and “pure melancholia”. Recognizing that polarity is not restricted to mood but extends to thinking, emotions, and motility, he also separates the “unsystematic schizophrenias” from the “systematic schizophrenias” and the “cycloid psychoses” from “manic depressive illness”. Then, with the employment of “totality”, Leonhard separates the “pure euphorias” from “pure mania” and the “pure depressions” from “pure melancholia”; and with the adoption of Wernicke’s “psychic structure”, based on the three components of the reflex, he divides the “cycloid psychoses” into “confusion” psychoses, “anxiety-happiness psychosis” and “motility psychosis”, the “unsystenmatic schizophrenias” into “cataphasia,” “affect-laden paraphrenia” and “periodic catatonia”, and the “systematic schizophrenias” into “paraphrenias”, “hebephrenias” and “catatonias.”**

Leonhard’s classification was published in 1957 just about the time that neuropsychopharmacology was born. Two years later, in 1959, Christian Astrup was first to show that patients with unsystematic schizophrenia respond more favourably to neuroleptics than patients with systematic schizophrenia.70 It was

---

* There are five forms of “pure euphoria”: unproductive, hypochondriacal, enthusiastic, confabulatory and non-participatory; and there are five forms of “pure depression”: harried, hypochondriacal, self-torturing, suspicious and non-participatory.

** There are six sub-forms of paraphrenia: hypochondriacal, phonemic, incoherent, fantastic, confabulatory and expansive; four sub-forms of hebephrenia: silly, eccentric, insipid and autistic; and six sub-forms of catatonia: parakinetic, affected, prokinetic, negativistic, voluble and sluggish.
also Astrup first, in the early 1960s to delineate the conditioned reflex profile of Leonhard’s different forms and sub-forms of schizophrenia.\textsuperscript{71,72,73}

During its first fifty years, inadequate classifications of psychiatric disease, disagreements about the means in which mental pathology is expressed, and lack of identification of treatment responsive forms of illness, have impeded progress in the field in spite of the major advances in some research areas.

**Interviewees and Interviewers**

Volume 9 includes transcripts of 19 videotaped biographic interviews. There are four MD, PhDs (Gottschalk, Donald Klein, Pletscher and van Praag), 12 MDs (Ayd, Ban, Berger, Cole, Fink, Hollister, Itil, Janowsky, Levine, Meltzer, Simpson and Sarwer-Foner), and three PhDs (Gittelman-Klein, Katz, and Kornetsky) among the interviewees. The 16 MDs (including the MD, PhDs) include 13 certified psychiatrists, one microbiologist (Berger), one internist (Hollister) and one pharmacologist (Pletscher). The three PhDs are psychologists.

All interviewees are ACNP members; seven (Ayd, Cole, Fink, Gottschalk, Hollister, Kornetsky and Sarwer-Foner) are Founders; and five (Cole, Hollister, Donald Klein, Meltzer and Simpson) are past-presidents.

All transcripts in Volume 9 are based on the second interview of interviewees, and all but six interviews were conducted at ACNP’s annual meetings from 1994 to 2008. From the six interviews conducted between annual meetings, five were done in Nashville, Tennessee, and one (Pletscher) at CINP’s biennial congress in Paris, France.

The 19 interviewees were interviewed by 12 interviewers: nine interviewers (Angrist, Belmaker, Braslow, William Bunney, Carpenter, John Davis, Koslow, Leckman and Tamminga), conducted one interview; 2 (Healy and Tone), conducted two, and 1 (Ban) six. From the 12 interviewers 10 are peers of the interviewees; and 2 are medical historians (Braslow and Tone). One of the medical historians (Braslow) is also a qualified psychiatrist.

By the time the editing of Volume Nine was completed, 6 of the interviewees (Ayd, Berger, Cole, Gottschalk, Hollister, and Pletscher) had passed away.

**Contributions of Interviewees**

In the following section some of the early and more recent contributions of interviewees to the development of neuropsychopharmacology are reviewed:

In 1947, *Frank M. Berger* observed that mephenesin has muscle relaxant and tranquilizing effects in animal.\textsuperscript{74} In 1949 he reported on the effect of the substance on spastic and hyperkinetic disorders.\textsuperscript{75} Berger’s determination to
synthesize and develop a mephenesin-like drug with a longer duration of action led in 1955, to the introduction of meprobamate for the treatment of anxiety disorders.76 During the 1950s and ’60s, Berger developed several other structurally similar propanediol preparations to meprobamate, e.g., tybamate.77 Yet, by the late 1970s Berger was no longer involved in psychotropic drug discovery and development. (See Berger also in Volume 3.)

In 1950 Conan Kornetsky was a member of Harris Isbell’s team that reported experimental findings in chronic barbiturate intoxication.78 In a subsequent report Kornetsky provided more details of his findings on the psychological effects of chronic barbiturate use.79 Kornetsky began with his research on the effects of anxiety and morphine on the anticipation and perception of painful radiating thermal stimuli in the early 1950s.80 During the years he extended the scope of his studies to the pharmacology of nociception, and in 2006, he reported that using thermal radiation and intra-cerebral electric stimulation, there was no difference in nociceptive threshold and analgesic response to morphine between old and young rats.81 In collaboration with Knapp, Tozier and Pak, he also revealed that medial forebrain stimulation enhanced intracranial nociception and attenuated morphine-induced analgesia.82 (See Kornetsky also in Volume 6.)

In 1954, Turan M. Itil was among the first to publish, in collaboration with Dieter Bente, on the effects of chlorpromazine (Megaphen) on the human EEG.83 During the 1950s, he also reported on the effect of promethazine on phantom pain84 and on EEG changes with several psychotropic drugs, e.g., reserpine, lysergic acid diethylamide.85,86 In the 1960s, Itil developed “quantitative EEG” with Max Fink and classified psychotropic drugs with the employment of the EEG.87 In the 1970s, he extended his research to the detection of psychotropic properties of drugs. It was in the course of this research that he discovered that the antidepressant properties of mianserin.88,89 By the 1980s, Itil employed “computerized EEG” also in predicting treatment response to psychotropic drugs, e.g., response to neuroleptics in schizophrenia.90 He continued his research with “computerized EEG” throughout the 1980s and 1990s. (See Itil also in Volume 6.)

In 1955, Alfred Pletscher, a member of Bernard Brodie’s team, in preparation for his new position with Roche, was first, to demonstrate in collaboration with Parkhurst Shore, that reserpine releases serotonin in the brain.91 In 1956 he had also shown that the monoamine oxidase inhibitor, iproniazid, increased cerebral serotonin levels.92 In the 1960s, as Roche’s research director, Pletscher was involved in the development of benzquinolazines, a series of reserpine-like monoamine depleting drugs with psychotropic effects.93 He was also instrumental in developing benserazide, an extracerebral decarboxylase inhibitor that enhanced the therapeutic effect of levodopa in Parkinson’s
disease.\textsuperscript{94} By the late 1970s Pletscher was no longer involved in neuropharmacology research. (See Pletscher also in Volume 3.)

In 1955 \textit{Leo E Hollister} was one of the first to report on the therapeutic effect of reserpine in the treatment of schizophrenia,\textsuperscript{95,96} and of Metrazol (pentylenetetrazol) and Hydergine in nervous and mental disease associated with old age.\textsuperscript{97,98} Hollister was also first to report in 1961 on withdrawal reaction after chlordiazepoxide discontinuation.\textsuperscript{99} During the 1960s and '70s Hollister was involved in studying the effect of numerous psychotropic drugs. The first edition of Hollister’s monograph on \textit{The Clinical Use of Psychotherapeutic Drugs} was published in 1973.\textsuperscript{100,101} As multi-center studies replaced single center clinical investigations in the 1980s, Hollister gradually withdrew from clinical investigations. (See Hollister also in Volume 1.)

In 1955 \textit{Gerald J Sarwer-Foner} was among the first in Canada, to study the use of reserpine and other psychotropic drugs in an “open psychiatric setting”.\textsuperscript{102} In 1956, he reported that instead of alleviating, reserpine and chlorpromazine enhanced anxiety in some patients.\textsuperscript{103} He attributed the paradoxical effect of these drugs to interference with ego defenses when “activity-passivity” mechanisms are involved.\textsuperscript{104} Throughout the years Sarwer-Foner has maintained that in patients’ response to psychotropic drugs psychodynamic mechanisms play a role.\textsuperscript{105,106} (See Sarwer-Foner also in Volume 1.)

In 1955 \textit{Frank J. Ayd, Jr.} published one of the first papers in the United States on the use of chlorpromazine in psychiatric patients.\textsuperscript{107} He became involved in clinical investigations with psychotropic drugs and in 1958 he reported on the differential effect of several phenothiazines.\textsuperscript{108} In 1960, Ayd was among the first to report on the antidepressant effect of amiriptyline.\textsuperscript{109} One year later, in 1961, he published his monograph on \textit{Recognizing the Depressed Patient}.\textsuperscript{110} About the same time, he also published the findings of his survey on neuroleptic-induced “extrapyramidal reactions”.\textsuperscript{111} In the mid 1960s Ayd launched \textit{International Drug Therapy Newsletter} to speed up dissemination of findings, with psychotropic drugs. In the 1980s Ayd gradually withdrew from clinical investigations and began with the preparation of his \textit{Lexicon of Psychiatry, Neurology and Neurosciences}. The Lexicon was first published in 1995.\textsuperscript{112} (See Ayd also in Volumes 1 & 10.)

In 1956 \textit{Louis A. Gottschalk} reported that in normal subjects response to pipradrol was more dependent on subjects’ personality traits than on any other factor.\textsuperscript{113} Subsequently, in the 1960s, Gottschalk studied the effects of several phenothiazines\textsuperscript{114} and benzodiazepines\textsuperscript{115} with the employment of his first “content analysis scales”.\textsuperscript{116,117} During the 1970s, Gottschalk became involved in pharmacokinetic research and studied the relationship between blood levels and clinical response of psychotropic drugs. It was in the course of these studies that he identified the metabolites of thoridazine and mesoridazine
responsible for the cardiac effects of these drugs. In 1980, Gottschalk reported his findings in toxicological and pathological studies on “drug-involved death”. Throughout the years “content analysis of speech” remained central in Gottschalk’s research. His instrument for “content analysis of speech” was translated into several languages and was used in studies with psychotropic drugs. (See Gottschalk also in Volume 1.)

In 1956 Jonathan O. Cole organized the first conference on Problems in the Evaluation of Pharmacotherapy in Mental Illness. Subsequently, he was the architect of the NIMH collaborative studies on the effectiveness of phenothiazine treatment in acute schizophrenia. In 1965, Cole co-authored paper with Gerald Klerman on the efficacy of imipramine and some other tricyclic antidepressants in depressive illness. During the 1980s, he collaborated with George Gardos in tardive dyskinesia research, and with Alan Schatzberg and Joseph Schildkraut in developing a biochemical classification of depression. (See Gardos and Schatzberg in Volume 3; Schildkraut in Volume 5.)

In 1990, with Teicher and Glod, Cole was first to report on the emergence of intense suicidal preoccupation during fluoxetine treatment. (See Cole also in Volumes 3 & 10.)

In 1957 Max Fink demonstrated the relation of Δ-activity in the human EEG and behavioral response to ECT. One year later, in 1958, Fink was among the first to report on the differential effect of antipsychotic, antidepressant and antianxiety drugs on the human EEG and behavior. In the same year, in collaboration with Shaw, Gross and Coleman, he showed the superiority of chlorpromazine to insulin coma therapy in the treatment of psychosis. During the 1960s and ’70s, Fink’s research was focused on pharmaco-EEG, digital computer analysis of the human EEG, and EEG classification of psychotropic drugs. In the 1990s his interest shifted and in 2003, he published his monograph with Alan Taylor on Catatonia, and in 2006 on Melancholia. (See Fink also in Volume 2.)

In 1961 Thomas A. Ban was among the first report on the psychomimetic properties of phencyclidine. He also noted that dose and pre-existing psychopathology determined the response to the substance. In his studies with psychotherapeutic drugs in the 1960s, Ban found no difference in therapeutic efficacy between pharmacologically different tricyclic antidepressants (e.g., desipramine and trimipramine) in depression, and between “incisive” and “sedative” neuroleptics (e.g., thiothixene and levomepromazine) in schizophrenia. Reviewing all available psychotropic drugs from structure – activity relationships to clinical effects in 1969 in his Psychopharmacology, Ban concludes that the pharmacological heterogeneity within psychiatric diagnoses is an impediment for progress in neuropsychopharmacology. In 1970 he introduced a conditioning test battery for the study of psychopathological
mechanisms and psychopharmacological effects, and in the 1980s and ‘90s he developed “composite diagnostic evaluations” for use in clinical investigations with psychotropic drugs. In 2005, Ban embarked on the development of “nosologic homotyping”, a methodology that can provide the most homogeneous psychiatric populations that psychopathology and psychiatric nosology can offer for neuropsychopharmacology research. (See Ban also in Volume 3.)

In 1962, Donald F. Klein discovered that imipramine reduced the frequency of panic attacks. He followed up this lead and in 1964 delineated two distinct drug responsive anxiety syndromes. Klein was among the first, in the 1960s, to recognize the importance of psychiatric diagnosis in predicting drug effects. In 1969, he published his text on Diagnosis and Treatment of Psychiatric Disorders, co-authored by John Davis. (See, John Davis, Volume 5). In the 1970s, with the employment of “pharmacological dissection,” Klein identified “endogenomorphic depression”. By that time he extended his research to children by introducing imipramine in the treatment of “separation anxiety”. In the 1980s, Klein re-conceptualized anxiety, and in the 1990s he formulated his hypothesis that “spontaneous panics” are “false suffocation alarms.” In 2010, his research team reported findings suggestive of the involvement of the endogenous opioid system in panic. (See Donald Klein also in Volume 3.)

In 1962, George M. Simpson was among the first to report on the antidepressant effect of desipramine. He was also among the first, in 1965, to report on withdrawal effects with phenothiazines. During the 1960s, Simpson was involved in clinical investigations with neuroleptics, including haloperidol, molindone, thiothixene. In 1970 he introduced with Scott Angus a rating scale for measuring the severity of extrapyramidal symptoms, developed a rating scale for measuring the severity of tardive dyskinesia, reported on differences in efficacy between 150 mg and 300 mg of imipramine in the treatment of hospitalized depressed patients, demonstrated the antipsychotic effect of clozapine, and became involved with Thomas Cooper in pharmacokinetic studies with psychotropic drugs. (See, Cooper, Volume 8.) He has continued his research, throughout the years; he published on the heterogeneity of the neuoleptic malignant syndrome in the mid-1980s, and studied dose-response relationships with clozapine in the late1990s. Simpson led the team that reported in 2006 on the efficacy and tolerability of ziprasidone and olanzapine in acutely ill patients with schizophrenia and schizoaffective disorder. (See Simpson also in Volume 3.)

In 1963 Herman van Praag published findings supportive of a relationship between monoamine oxidase inhibition and antidepressant effects, and in 1965, he proposed a structured interview for diagnosing the “vital depressive
syndrome”. In 1970, Van Praag was among the first to report changes in cerebrospinal fluid 5-hydroxyindoleacetic acid levels in depressed patients with the employment of probenecid. By the mid-1980s, Van Praag became a proponent of “denosologization” of psychiatry. Yet, he has continued with his research and in 2002 published findings on Stress, the Brain and Depression, in a monograph co-authored by de Kloet and van Os. (See Van Praag also in Volume 5.)

In 1965 Martin M Katz was among the first in the United States to address the methodology of classifying psychiatric diseases. In 1969 he published findings on the influence of symptom perception, past experience and ethnic background on diagnostic decisions. By the end of the 1970s, the focus of Katz’s research shifted to the psychobiology of depression. In 1987 his team was first to challenge pharmacological findings that indicate a two to three week time-lag between initiation of treatment and antidepressant effects. Subsequently, in 1994, they published findings on the relationship between drug induced actions on neurotransmitter systems and changes in the behavior and emotions of depressed patients, in 2004, on the onset and early behavioral effects of pharmacologically different antidepressants, and in 2010, on “links” between neural and behavioral changes in the course of treatment of depression with antidepressants. (See Katz also in Volumes 3 & 10.)

In 1969 Jerome Levine co-authored paper with Arnold Ludwig, Louis Stark and Robert Lazar on negative findings with LSD-25 in the treatment of alcoholism and in 1971, he co-edited book with Burtrum Schiele and Lorraine Bouthilet on Principles and Problems in Establishing the Efficacy of Psychotropic Drugs. In the mid-1980s Levine developed SAFETEE, in collaboration with Nina Schooler, for the systematic assessment of side effects in clinical trials with psychotropic drugs, in the 1990s he became involved in the utilization of neuroleptics, and in 2002 he co-authored paper with A. Jaffe, on an analysis of neuroleptic use from 1994 to 2000 in a state hospital system. (See Levine also in Volume 3.)

In 1969 Herbert Y Meltzer reported on state dependent elevation of serum creatine phosphokinase and aldolase activity in acute psychoses and newly admitted schizophrenic patients. In the 1980s, Meltzer was member of the team that demonstrated the effectiveness of clozapine in some treatment resistant patients with schizophrenia, and in the 1990s of the team that showed improvement in cognitive functions with the substance in some similar patients. In 1989 Meltzer was first to classify, in collaboration with Matsubara and Lee, typical and atypical neuroleptics on the basis of dopamine-D1, D2 and serotonin pk1 values. Subsequently, he led the team of the “international
suicide prevention trial” that reported reduced suicidality in clozapine treated patients with schizophrenia in 2002.202 (See Meltzer also in Volume 5.)

In 1971, David S. Janowsky reported on monoamines and ovarian-hormone-linked sexual and emotional changes.203 One year later, in 1972, based on findings with physostigmine, he formulated a cholinergic-adrenergic hypothesis of mania and depression.204 In 1973 Janowsky demonstrated that methylphenidate provokes exacerbation of symptoms in some schizophrenic patients.205 Continuing with his research throughout the years in 2003 Janowsky published findings on the effect of antidepressants, methylphenidate and amphetamine on depression and dysphoria induced changes on the interpersonal perception of moods and caring relationship,206 in 2007 discussed the possible use of scopolamine as an antidepressant,207 and in 2008 reported that relapse after antipsychotic withdrawal predicts future relapses in institutionalized adults with severe intellectual disability.208 (See Janowsky also in Volume 5.)

In 1973, Rachel Gittelman Klein discussed the diagnosis of “school phobia” in light of its responsiveness to imipramine.209 In 1976 she led the team that reported on comparative effects of methylphenidate and thioridazine in hyperkinetic children.210 In 2008 Gittelman-Klein co-authored paper with Monnuzza and Moulton that reported on lifetime criminality among boys with ADHD.211 In 2010 she was member of the team that reported carbon dioxide hypersensitivity in separation anxious offspring of parents with panic disorder.212 (See Rachel Klei also in Volume 7.)

Volume 9 is the second volume in this series edited by Barry Blackewll, a distinguished psychopharmacologist, whose discovery of the cheese reaction with monoamine oxidase inhibitors in the 1960s had a major impact on the development of pharmacotherapy of depression. Part of Blackwell’s Introduction is based on quotations from interviewees’ reflections on developments in neuropsychopharmacology, and particularly on developments in research in the pharmacotherapy of psychiatric disorders, in the past fifty years.

REFERENCES

43 Fish F. Clinical Psychopathology. Bristol: John Wright and Sons; 1967.
55 Sauvages de la Croix FB. Nosologia Methodica. Amsterdam: Frat de Tournes; 1768.
60 Faiet JPF. De la folie circulaire. Bul Acad de Méd (Paris) 1854; 18: 382-400.
64 Bleuler E. Dementia praecox oder groupe der Schizophrenien. Leipzig: Deuticke; 1911.
76 Berger FM. The pharmacodynamic properties of 2-methyl-2-n-1, 3 popanediol dicarbamate (Miltown), a new interneuronal blocking agent. J Pharmacol Exp Ther 1954; 112: 413-23.


Preface


158 Klein DF. False suffocation alarms, spontaneous panics, and related conditions; An integrative hypothesis. Arch Gen Psychiatry 1993; 50: 306-17.


CONTENTS

Preface, Thomas A. Ban ix
Abbreviations xxxiii
Introduction, Barry Blackwell xxxvii

Interviewees & Interviewers

Frank J. Ayd, Jr. 3
   interviewed by David Healy
Thomas A. Ban 19
   interviewed by William E. Bunney, Jr.
Frank M. Berger 37
   interviewed by Thomas A. Ban
Jonathan O. Cole 57
   interviewed by Thomas A. Ban
Max Fink 73
   interviewed by David Healy
Louis A Gottschalk 105
   interviewed by Thomas A. Ban
Leo E. Hollister 135
   interviewed by Thomas A. Ban
Turan M. Itil 171
   interviewed by Andrea Tone
David S. Janowsky 183
   interviewed by Burt Angrist
Martin M. Katz 193
   interviewed by Stephen M. Koslow
Donald F. Klein 205
   interviewed by John M. Davis
Rachel G. Klein 221
   interviewed by James F. Leckmann
Conan Kornetsky 233
   interviewed by Thomas A. Ban
Jerome Levine 243
   interviewed by William T. Carpenter, Jr.
Herbert Y. Meltzer 257
   interviewed by Carol A. Tamminga
Alfred Pletscher 269
    interviewed by Andrea Tone
Gerald J. Sarwer-Foner 277
    interviewed by Joel Braslow
George M. Simpson 285
    interviewed by Thomas A. Ban
Herman M. van Praag 313
    interviewed by Robert H. Belmaker

Index 321
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAAS</td>
<td>American Association for the Advancement of Science</td>
</tr>
<tr>
<td>ACNP</td>
<td>American College of Neuropsychopharmacology</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ADAMHA</td>
<td>Alcohol, Drug Abuse, Mental Health Administration</td>
</tr>
<tr>
<td>AGP</td>
<td>Association for Documentation of Psychopathology in Gerontopsychiatry</td>
</tr>
<tr>
<td>AIDS</td>
<td>autoimmune deficiency syndrome</td>
</tr>
<tr>
<td>AMDP</td>
<td>Association for Methodology and Documentation in Psychiatry</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>ASC II</td>
<td>American Standard Code for Information Exchange</td>
</tr>
<tr>
<td>BDH</td>
<td>British Drug Houses</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CATIE</td>
<td>Clinical Antipsychotic Trials of Intervention Effectiveness</td>
</tr>
<tr>
<td>CIA</td>
<td>Central Intelligence Agency</td>
</tr>
<tr>
<td>CIANS</td>
<td>Collegium Internationale Activitatis Nervosae Superioris</td>
</tr>
<tr>
<td>CIBA</td>
<td>Chemical Industry in Basel. (Swiss pharmaceutical company.)</td>
</tr>
<tr>
<td>CINP</td>
<td>Collegium Internationale Neuropsychopharmacologicum</td>
</tr>
<tr>
<td>CMHA</td>
<td>Canadian Mental Health Association</td>
</tr>
<tr>
<td>CODE – DD</td>
<td>Composite Diagnostic Evaluation of Depressive Disorders</td>
</tr>
<tr>
<td>CODE – HD</td>
<td>Composite Diagnostic Evaluation of Hyperthymic Disorders</td>
</tr>
<tr>
<td>CRO</td>
<td>clinical research organization</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computerized tomography</td>
</tr>
<tr>
<td>DCR</td>
<td>Diagnostic Criteria of Research</td>
</tr>
<tr>
<td>DSS</td>
<td>Double Simultaneous Stimulation</td>
</tr>
<tr>
<td>DST</td>
<td>dexamethasone suppression test</td>
</tr>
<tr>
<td>ECDEU</td>
<td>Early Clinical Drug Evaluation Units</td>
</tr>
<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram</td>
</tr>
<tr>
<td>EKG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EPS</td>
<td>extra pyramidal symptoms</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (USA)</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine (serotonin)</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>serotonin 2 receptor</td>
</tr>
<tr>
<td>GABA</td>
<td>y-amino butyric acid</td>
</tr>
</tbody>
</table>
GUIDE Chronic Schizophrenia: A Guide to Leonhard’s Classification
HDL high density lipoprotein
ICT insulin coma therapy
IRB Institutional Review Board
IV intravenous
LDH low density lipoprotein
LISP (An early family of computer programming languages)
LSD lysergic acid diethylamide
MAO monoamine oxidase
MAOI monoamine oxidase inhibitor
MDNA mitochondrial DNA
MIT Massachusetts Institute of Technology
MNI Montreal Neurological Institute
MRC Medical Research Council (UK)
MRI magnetic resonance imaging
NAS National Academy of Science
NASNRC National Academy of Science National Research Council
NE nor epinephrine
NIAA National Institute of Alcohol Abuse and Alcoholism
NICHD National Institutes of Child Health and Human Development
NIDA National Institute on Drug Abuse
NIH National Institutes of Health
NIMH National Institute for Mental Health
NOSIE Nursing Observation Scale for Inpatient Evaluation
NYU New York University
OH hydroxyl (group)
OL opinion leader
PET positron emission tomography
PSCL Psychopathological Symptom Check List
QPRA Quebec Psychopharmacological Research Association
REM rapid eye movement
RO1 investigator initiated research project grants that meet an Institute’s defined mission
SAPD Social Alienation Personal Disorganization Scale
SKF Smith, Kline and French (Pharmaceutical Company)
SSRI selective serotonin re-uptake inhibitor
STP 2,3 dimethoxyamphetamine
T-32 five year training grants in specific disciplines for graduate students or fellows
TD tardive dyskinesia
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>tetrahydrocannabinol</td>
</tr>
<tr>
<td>TMS</td>
<td>trans-magnetic stimulation</td>
</tr>
<tr>
<td>TPQ</td>
<td>Three Dimensional Personality Questionnaire</td>
</tr>
<tr>
<td>TRH</td>
<td>thyroid releasing hormone</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UCI</td>
<td>University of California at Irvine</td>
</tr>
<tr>
<td>UCLA</td>
<td>University of California at Los Angeles</td>
</tr>
<tr>
<td>UCSD</td>
<td>University of California at San Diego</td>
</tr>
<tr>
<td>UNC</td>
<td>University of North Carolina</td>
</tr>
<tr>
<td>USPHS</td>
<td>United States Public Health Service</td>
</tr>
<tr>
<td>VCTB</td>
<td>Verdun Conditioning Test Battery</td>
</tr>
<tr>
<td>VPH</td>
<td>Verdun Protestant Hospital</td>
</tr>
<tr>
<td>VPTB</td>
<td>Verdun Psychometric Test battery</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
INTRODUCTION  
Barry Blackwell

This Volume includes 20 interviews. These consist of second interviews conducted between 1997 and 2008, the majority (13 interviews), in the first decade of the 21st century. Earlier first interviews and biographies are contained according to topic in the following volumes: Volume 1, Ayd, Gottschalk, Hollister and Sarwer-Foner; Volume 2, Fink and Itil; Volume 3, Berger, Janowsky and Pletscher; Volume 4, Ban, Cole, Katz, Donald Kline, Levine and Simpson; Volume 5, Van Praag; Volume 6, Kornetsky; Volume 7, Rachel Kline, Costa and Kaufman.

The purpose of these second interviews was to focus less on each person’s considerable accomplishments but to obtain an overview of the field from its leading pioneers. This would include its accomplishments and shortcomings as well as future hopes and expectations. The Volume is a gold mine of hard earned wisdom distilled from lifetimes of experience.

Two of those interviewed were part of the original six member ACNP organizing committee (Ayd and Cole) and eight were founding members in 1961 (Ayd, Cole, Costa, Fink, Gottschalk, Hollister, Kornetsky and Sarwer-Foner). Four became Presidents of the ACNP over a span of a quarter century (Cole ’66, Hollister, ’74, Don Klein, ’81, and Simpson, ’91) and another three served as Council members (Ayd, Costa and Kornetsky). Five were recipients of the Paul Hoch Distinguished Service Award (Ayd, Ban, Cole, Hollister and Don Klein).

As the ACNP approaches its fiftieth anniversary in 2011 it is sad but inevitable to note that seven of those interviewed are deceased, four in the last two years.

This Volume is dedicated to Nathan S. Kline who was both a founding member of the ACNP and its sixth President (1967). Unfortunately Dr.Kline died at the early age of 67 in 1982 before this history project was initiated. There is nobody who better personifies the pioneering spirit that initiated the field of psychopharmacology. “Nate” was intensely energetic, creative, curious, challenging, provocative and entrepreneurial. The interviews of George Simpson and Leo Hollister offer insights into his personality and accomplishments. In 1952, at age 38, he started a research unit at Rockland State Hospital in New York, named the Nathan S. Kline Institute after his death. He initiated the use of reserpine in schizophrenia and then chlorpromazine. Among the first also to use tricyclic antidepressants and the MAO inhibitors; his research team
recognized the potential link between clinical and biochemical mechanisms. For these accomplishments he twice won the prestigious Albert Lasker Award.

Nate was a researcher, busy practitioner, publicist, politician and world traveler. His popular book, *From Sad to Glad* is still in print and available on Amazon. He published over a hundred scientific articles and is credited with lobbying the Congress to originate Federal funding for psychopharmacology research. (See, Katz). For better or worse the results he obtained at Rockland State Hospital helped to trigger the process of deinstitutionalization for people suffering from severe mental illness.

Characteristics of those interviewed in this volume reflect the scientific and cultural Zeitgeist of the mid-1950s. They include only one woman, Rachel Klein, who became a member of the ACNP in 1973. Clinicians far outnumber basic scientists. Two were devoted mainly to neuropharmacology (Berger and Pletscher). Today the ACNP membership is split almost equally between MDs and PhDs. Three of the clinicians are psychologists (Katz, Kornetsky and Rachel Klein) and the remainder physicians. In analyzing the content of these interviews extensive use will be made of the scientist’s own words to illustrate the themes that emerge.

While every one of these scientists is distinguished in the field, different career patterns are apparent. Two clinicians stressed the diversity of their contributions. Hollister says, “I can’t point to a single real discovery in the sense of something vastly new or revolutionary. I attribute it partly to my free will, to the freedom I’ve been given to follow wherever I wanted to go, which tends to make you more diffuse compared to somebody who says I’m going to focus on something and find the answer”. In the same vein Janowsky states, “My career has been unusual in one way. I’ve done a number of different things at different times and I haven’t done any one in great depth”. Later he adds, “I liked the idea of being an innovator, getting in and getting out; of course that has a strong disadvantage, because the ethos of science is linear and in depth”.

Contrast this diverse approach with the focused one shown in the lifelong career devoted to identifying the causes of phenylketonuria by Kaufman. These examples separate two distinct career patterns but clearly there are also hybrid forms. In his interview of Don Klein, John Davis applauds the persistence that led to the discovery and definition of panic disorder, its treatment and potential biochemical etiology, work he considers, “of Nobel Prize caliber”. But Don Klein has also made many other contributions to the field, including the phenomenology of “atypical depression” and childhood “asocial schizophrenia”, the technique of “pharmacological dissection” and the virtues of “specialty clinics” to focus on the nosology of different disorders.

These interviews also make the reader aware of the climate for innovation involved in a scientific paradigm shift. Don Klein comments, “At the time I went
to medical school from 1949 to 1952 I believe every Chairman of Psychiatry in the United States was a psychoanalyst”. It required courage for a young scientist to challenge that Zeitgeist. As Don Klein also notes, “when I told my analyst in 1959 I was going to Hillside Hospital to study drugs in clinical trials he said, “that is your sadism”.

But not every budding psychopharmacologist had to be a Don Quixote. Some of these same psychoanalytic Chairmen were supportive and nurturing toward the new discipline. Among those interviewed are analysts who displayed a creative adaptation to the advent of drugs. Two were founding members of the ACNP in 1961. Sarwer-Foner, who graduated from medical school in 1951, became a lifelong friend of Delay and Deniker who pioneered chlorpromazine. He practiced a unique form of individualized psychiatry that combined analytic and pharmacological insights and observations, “I felt these drugs were not, in essence, curative but they could be used for their pharmacological action. If chlorpromazine made you tired or weak it was going to be good for agitated patients … if a drug gave you more energy and made you outgoing this would be good for somebody who felt weak, tired, helpless or exhausted, such as certain obsessionals or depressives”. Not only would later controlled studies confirm this clinical speculation but the close observation of symptomatic response in individual patients was prescient of Don Klein’s “pharmacological dissection”.

Another impressive example of innovative adaptation is the career of Lou Gottschalk who preceded me on the faculty of the University of Cincinnati. Lou graduated from medical school in 1943 and, after the war ended, did graduate work and psychoanalytic training in Chicago at a time when, “the University of Illinois and the University of Chicago both gave doctorates in Neurophysiology and for some reason, didn’t see any incompatibility between psychoanalysis and neurophysiology”. After a stint at NIMH and winning the Hofheimer Award, Lou began his lifelong research into verbal content analysis; “I like to listen to language. How do psychiatrists learn anything about anybody?” As an adult and child training analyst he was also able to say, “Science has to have a statistical basis for its assertions to be valid; otherwise they are a matter of faith”. As a scientist he was able to say, “We proved we could do content analysis of language, made headway in reliability and validity and computerized the methodology”.

Collectively these interviews reflect a rewarding environment that reinforced innovation and enquiry. As Frank Ayd noted, “I was in it when it was the best time to do research”. It was a time when attention focused sharply on each patient’s response to promising new treatments.

The methods to study this new field were exciting and novel. Hollister comments, “Back when John Overall and I were working and nobody knew what
the best ways were to give the drugs, what were the best way to use rating scales or what were the best statistical procedures it was something you could contribute that was original and scientific”.

When everything is new ignorance is an asset, free of pre-existing misconceptions. Rachel Klein reports her earliest impressions in the new field, “The ethos of the research department was that we knew little. I was very impressed with this ability to acknowledge ignorance”.

Pletscher was more specific about the stimulating appeal of an intellectual vacuum. “At that time (1954), people had no idea of what causes depression, euphoria or anxiety and nobody knew anything about the mechanism of action of the psychotropic drugs”. The lure of this novel field was not only intellectual, it was commercial. Pletscher continues, “When I returned from the NIH to start my job with Hoffman La Roche in Basel I told top management that the primary area of research must be psychotropic drugs because that was the upcoming field”. Frank Berger was more succinct, “They (management) wanted me to find drugs with a big market”. And so he did, with meprobamate (Miltown).

The atmosphere surrounding the early researchers was cozy and convivial. Simpson remembers, “At that time (late 1950s) I knew every psychopharmacologist in the country. There was camaraderie and a fair amount of fun”.

It was not only the drugs and the research strategies that were new, so were the patients and the positive feedback they provided physicians. Simpson continues, “Those patients had never used drugs before and you really did see people who would tell us they felt better than ever in their whole life. They improved dramatically”. Positive feedback was scientific as well as psychosocial. Study populations were naïve, uncontaminated and not saturated with treatment resistant individuals. New basic science techniques also yielded novel findings. As a result Van Praag notes, “There were new discoveries almost every month, so it was a very exciting time”.

Individually and collectively the interviews convey the exciting climate and hopes for the new field of psychopharmacology. What do they also say about the changes and outcomes fifty years later? Even after subtracting for nostalgia it would be Pollyannaish to deny some discontent, disappointment and frustration. Things were not as simple or predictable as the pioneers had hoped or expected.

Despite a plethora of rating scales, diagnostic check lists and statistical techniques clinical trials were largely unable to distinguish between drugs even when they had different neurochemical actions. Listen to Hollister, “To find the right drug for the right patient has been a very frustrating experience … it may be that the questions you ask determine the answers you get and when you use these instruments all you are doing is codifying the mental status exam and the questions determine what area of psychopathology you learn about”.


Turan Itil laments, “We don’t know the cause of any psychiatric illness and therefore we don’t have a real treatment for any of them”. Janowsky identifies another flaw, “We’ve thrown away a lot of things that are important in research by worshipping the god of obsessionality … the person who wants to look in a decidedly different direction is often considered ‘out to lunch’”.

Katz believes that these barren outcomes are because trial methodology supports a commercial rush to establish efficacy more than close clinical attention to therapeutic process. “Why have we not completed the story about how these drugs operate therapeutically in patients? There has been little examination for years of the series of behavioral events that happen in the first week. Clinical trials appear to dictate that the investigators only want to know what happened in four to six weeks since that tells you whether a drug is effective in treatment. As long as we adhere to the mechanical trial method for how drugs achieve their therapeutic effects we are not going to learn anything new”.

Errors in logic can compound flaws in observation as Don Klein notes, “They think if two conditions both respond to the same drug it must be the same condition”.

Complexity also trumps simplicity at the biochemical level. Costa (see, Volume 7) states this eloquently, “One receptor does many different things than just the one you’re interested in … drugs that are successful are those that target three or four receptors”. And even more succinctly, “No transmitter regulates a particular function”.

Those addicted to Occam’s razor or the lure of simple unifying models learned to be disappointed. As Itil puts it, “Every ten years we have another hypothesis for depression. In my lifetime we have had four different hypotheses, obviously none of them is true”.

Doing things for all the right and necessary reasons often has unwanted effects. The paradigm shift from a psychoanalytic to a psychopharmacologic model demanded a nosologic revolution to better know and recognize what we were treating and a scientific shift from opinions based on anecdotal case studies to trial designs that protected us from bias and erroneous conclusions. The harm drugs could inflict also invited regulatory standards and oversight.

So, rating scales, the DSM system, double-blind controlled studies, complex statistical analysis and the FDA were all natural and desirable developments that brought their own downside. On the positive end hundreds of thousands of people who had suffered for centuries in mental institutions and prisons or could not afford or benefit from the luxury of psychoanalysis now had access to medicines that helped even if they didn’t heal. But this too came at the cost of an expanded and pervasive role for the pharmaceutical industry bringing with it conflicts between commerce and science. These benefits and costs are reflected in the interviews.
The rating scales and statistical techniques that became part of standard clinical research were sometime ambivalently viewed. Ban states, “For me changes in the psychopathological symptom profile of individual patients were far more informative than changes in rating scales.” Statistics were not always helpful, “We had numerous statistically significant findings but none of them was of clinical significance”. Statistical fads replaced old fashioned ways of evaluating data but were not always an advance in Don Klein’s opinion, “Extremely detailed literature review has been replaced by meta-analysis, which is much worse in every way, though it has limited uses”.

Long the gold standard, limitations of conclusions drawn from double blind controlled studies became apparent. Their short duration, highly selected but relatively small patient samples and unnatural compliance highlighted the distinction between efficacy and effectiveness shown in the CATIE study, including the failure to detect long term side effects or make valid comparisons with older and cheaper standard drugs. Fink tells us, “I have stopped using any drug produced after 1980. None has been tested independently and with time their inefficacy and risks are better understood”.

Among the most frequent causes for concern are shortcomings in the DSM system. Several flaws are identified. Perhaps the most succinct criticism comes from Hollister, “Anytime things get standardized, that’s an excuse to stop thinking”. In my own work environment there appears to be an epidemic of “Depression, NOS”. Rachel Kline elaborates on this concern, “I’m a little disappointed, I should say more than a little in how the DSM is used. We had great hopes it would alter our approach to patients. It has not fulfilled its promise. We have adopted a check list approach to diagnosis and the sense of what has gone wrong has been lost. The DSM was never intended to be a formula or rule. It was to be a guide for clinical purposes”.

Don Klein has a different concern, “DSM has deflected clinicians away from taking detailed developmental histories … many, including scientists, made the unwarranted assumption that these clearly heterogeneous syndromes could be handled as if they had a homogeneous etiology”. Don supports this criticism by drawing attention to his work on atypical depression’s selective response to MAO inhibitors. He points out that pharmaceutical companies “prefer a broad syndrome because that is what the FDA approves and you have a much bigger market so it is counter productive from their point of view to refine syndromes”. He also expresses the opinion that it is not only the FDA and industry that have adopted the DSM for drug evaluation but, “I don’t think the NIMH has been supportive of the effort to subdivide syndromes experimentally to detect specific pathophysologies”.
The most cogent scientific objection to such use of DSM is given by Van Praag, “If we use DSM diagnostic entities we will never progress in biological psychiatry. It would be an absolute miracle to find the cause of schizophrenia”.

Katz gives an excellent summary of all these concerns, “The DSM system has become an impediment and could be a misleading influence on the design of future research. If we don’t transfer reliance on that diagnostic system to changes in behavior, mood and cognitive function we will never learn the nature of the elemental interaction between chemistry and behavior that determines what is going on in the therapeutic process”.

Another broad category of concern is not just the scientific design of clinical trials but the shifting role of individuals, the NIMH and industry in organizing and supporting them. At the very beginning of psychopharmacology the earliest studies were often uncontrolled observations by astute clinicians like Ayd and Sarwer-Foner. As the field developed sophistication some adopted a more scientific approach while others were forced to quit. Ayd comments, “What a company has to produce to help satisfy the FDA’s requirements has made it literally impossible for people like me to be researchers anymore”.

Clinicians working in State or VA hospitals, like Hollister and Simpson, were sometimes able to obtain institutional support for research and, in the early days, industry often supported individual projects. But this was a piecemeal approach that did not satisfy the need for a cadre of dedicated and well trained clinical researchers. Don Klein notes that, “if you don’t get grants you have to disperse your team, so doing long term, intensive work becomes impossible”. There were also gaps in industry support due to commercial disincentives. Rachel Kline notes the absence of support for pediatric psychopharmacology; figuratively and literally a “small” market. Lou Gottschalk comments wryly on industry’s disinterest in studying side effects.

These dilemmas were partly resolved when the NIMH established the Early Clinical Drug Evaluation Units (ECDEU) program first under the leadership of Jonathon Cole and then Jerry Levine. Even here there were trade offs, as Levine notes, “The FDA started to want guidelines for clinical trials … and the existence of the ECDEU way of studying medications using standardized forms became the basis of what they required. The danger of that is you rigidify the field so that everybody does studies in exactly the same way”. Why the NIMH shut down the program is unclear but may be related to the lack of clinical progress and, as Don Klein notes, “NIMH has gone very basic. They are primarily researchers at an animal or cellular level. I don’t know how they’re going to reverse that because it has a lot of cache”.

With the withdrawal of Federal support the management of clinical trials became almost entirely the responsibility of industry. As Itil notes, “When the Early Clinical Drug Evaluation program was dissolved investigators became
dependent completely on drug companies”. The results have not met with the approval of several of those interviewed for this volume. Don Klein is concerned because, “one of the biggest missing pieces in current psychopharmacology is adequate Phase Two studies. Because industry can’t use that work as definitive for the FDA, it doesn’t work and drugs are rushed through”. Janowsky is outspoken, “The value system has become money and technique bound, as opposed to discovery bound. I think the value system is sick”. Simpson comments in detail, “Pharmaceutical houses design the studies, their staff manages the data and clearly nobody is totally free of bias. I think it was that kind of thing the NIMH tried to prevent”. Hollister concurs, in his inimitable salty language, “It’s all become so standardized that the drug companies have big groups of people designing protocols, rating scales and report forms, analyzing statistics. It reduces the investigator to a mere peanut gallery and most of the studies are done by flunkies they hire so there’s no scientific input at all. Well, that’s a hell of a way to do things!”

The interviews reflect a concern about the profit motive that is ubiquitous and extends beyond drug research. Janowsky states, “We’ve gone overboard and embraced a value system that’s high tech and money oriented and that has perverted the fun of it all”. Kornetsky agrees, “I would like to see more attention paid to science and less to money. What is driving science now is not the excitement but something else and it’s bothersome”.

From within industry Pletscher provides an example, without apology, “We were expected to keep in the back of our mind that we had to bring in money to do what we wanted to do. This was the reason I did not pursue my interest in developing drugs against malaria or tropical sleepiness and decided we should work on the development of treatment for depression and schizophrenia”. In judging such a statement it must be remembered that the size of a market is proportional to the size of the population in need.

The influence of direct advertising on prescribing practices and public demand leads Simpson to say, “It was a smart marketing ploy of Lilly to go after non-psychiatrists with the newer drugs. Of course only 25% of psychotropics in the United States are prescribed by psychiatrists. So they went where the money is”. Later, he adds, “There is a terrible influence on the whole of medicine, the marketing of products that goes on. That has been escalating”. Berger, a former director of industry research agrees, “I feel physicians should go to the real sources of information about the drugs they are using and should not get acquainted from laymen that have vested interests”.

This concern extends to every source of information for physicians; medical schools, conferences and seminars, national, regional and local. Fink, who describes himself as “A Don Quixote figure” expresses this as follows, “The APA has now been taken over by industry. The ACNP has made an attempt, I
understand, to deal with the issue but leaders of the society are intimately tied to industry”. Janowsky believes, “We have become perverted as a system at the natural level in our own minds and in our universities”.

Hollister draws attention to the influence of industry support on advocacy organizations, “Advocacy organizations are claiming this is a magnificent new era in psychotherapeutic drugs. Now you know where that orchestration is coming from. It’s very well organized by drug companies because they would like nothing more than to have these declared first line drugs”. Hollister continues on to identify a telling practical consequence of inflating the efficacy of newer more expensive drugs, “I think we’re buying a lot of expense we don’t need ... if you’re buying expensive drugs and have to give up the rest of treatment, that’s a bad bargain”.

Taken together these interviews express disappointment that the early excitement and productivity has dwindled and some hopes have not been fulfilled. The field has increased in size, complexity and scope with an inevitable loss of intimacy and collegiality. Meaningful clinical advances have been few and far between and basic science has proliferated to fill the vacuum and absorb the resources. Commerce and deregulation have exerted an increasing influence with minimal evidence of better outcomes.

But are there misgivings or regrets over and above those already expressed? There is a sense of promising ideas prematurely abandoned. Ban mentions early work on conditioned response variables that, “Might provide a bridge between psychopathology and neurophysiology”. He also advocates for the predictive value of Leonhardt’s classification of the psychoses as does Van Praag for a “Vital depressive syndrome” both of which held more promise of revealing an underlying biochemical etiology than the DSM system. Fink regrets that electrophysiology was, “Pushed into the background and, suddenly, everybody was involved with neurotransmitters. The pharmaco-EEG world ended about 1990”. Itil adds, “Looking at the effect of a substance on the electrical activity of the brain is the simplest method of identifying the potential therapeutic profile of a drug”. Gottschalk continues to advocate for verbal content analysis, “It looks like it is much more sensitive than any other kind of psychiatric assessment”.

Some attrition of promising techniques could be attributed to the fact the field was in a hurry and to resulting changes in funding priorities. Janowsky notes, “Productivity, as it is now called, should not be based on whether you get a grant or not, but on whether you make a discovery”. He also reminds us that, “Some of the better discoveries lately, like the mood stabilizers for bipolar disorders, didn’t come out of some high tech device. They came out of somebody making clinical observations; those are very important and undervalued”.

In addition to the dominance of basic neuroscience mentioned by Fink and others Levine points to changes in NIMH funding procedures that have reduced feedback, “The field has suffered because of it and it is something we need to get restarted”. In response to the degradation in clinical trials and industry’s economic influence Simpson goes further and suggests resurrecting the federally funded ECDEU system of clinical investigators.

The interviews mention other promising areas of research that might have been pursued with benefit and could be re-examined; Katz states, “I would like to see us getting back to examining the effects of psychedelic agents. They had such unusual effects on memory, perception and learning but we have no way of knowing what they might tell us about the mind, its potential and limits”. Don Klein regrets the failure of more widespread adoption of “pharmacological dissection” to probe for clinical entities linked to pharmacologic responses.

Hopes for the future of psychopharmacology are tinged with the skepticism experience has imposed. Levine admits, “I am a bit cautious about how soon we will have a dramatic breakthrough that will change our field. We have new tools; we have genetic and imaging techniques and we have learned a tremendous amount, but we haven’t been able to hit a home run.” Simpson concurs, “I would like to see genetic links to all the major illnesses. I think we are a long way from that, but the technology seems to be there”. Janowsky is also hopeful of genetics but urges more attention to personality traits, “Profiling the genes in terms of personality rather than symptoms”.

Simpson offers a common sense plea that in opting for neuroscience we not throw out the clinical baby with the bathwater, “It’s easy to focus on these new methods and under estimate the value of clinical contributions. To do a good clinical job takes a long time and it’s not certain you’ll be rewarded. But if you can’t spend the time all the science in the world would just create confusion”. This resonates with Ayd’s sage comment, “It takes time to get past the glow of the initial benefit and begin to look realistically at what a drug is really doing”.

Viewed over a fifty year time span this volume illustrates how the pace of drug discovery ebbs and flows as serendipity and coincidence interact with the yin and yang of clinical and basic science. While that balance may have shifted it is well to remember that animals are not humans and, to be useful, neurochemistry needs to be correlated with feelings, thoughts and behavior. The interviews express concerns that our capacity to accomplish this translation has been blunted and dulled by a decline in the quality of clinical drug evaluation. This is surprising at a time when one in six ACNP members has both an MD and a PhD and one in twenty are representatives of industry.

The comments of pioneers in the field point to a number of cumulative factors that contribute. These include inadequate contemporary trial design and
implementation, an insensitive DSM nosology, commercial influences on the conduct, educational interpretation and dissemination of research to the public and professionals, and minimal FDA criteria for drug approval. It is tempting to conclude that psychotropic drug development is in a recession, harmed like our economy and environment (2011) by the undue influence of short term commercial goals and lax regulatory oversight.

It is as if industry is slowly but unwittingly killing the goose that lays its golden eggs. Despite this gloomy conclusion, those who have devoted their life span and careers to psychopharmacology have few, if any, regrets. This introduction to their interviews ends with quotations from two of the pioneers.

Janowsky sums his career up by saying, “It never felt like work or that I was doing it for money. Somebody was paying me to do the things I would probably have done as a hobby.” Levine echoes that sentiment, “There are a lot of definitions of utopia and mine is when someone will pay you for the work you love to do; that’s how I feel about psychopharmacology.”

Whatever the accomplishments of the fifty years will be, these sentiments by the current pioneers would be, a benediction greatly to be desired for future generations of psychopharmacologists.
INTERVIEWEES & INTERVIEWERS
FRANK J. AYD, Jr.  
Interviewed by David Healy  
Las Croabas, Puerto Rico, December 13, 1998

DH: It is December 13, 1998. We are in Puerto Rico and on behalf of ACNP I will be interviewing Frank Ayd. I’m David Healy. Before chlorpromazine came out you should have had reserpine for a short period. Did you get into chlorpromazine because of your SKF contacts?

FA: I got into chlorpromazine first, and CIBA approached me shortly after that about reserpine. Nate Kline probably was responsible. We had worked together on some projects for the VA and knew each other. Now, it was a very difficult drug with a lot of undesirable side effects apart from the hypotension, which were real; the nausea, the vomiting, the drooling and so forth. And it caused extrapyramidal symptoms at a more frequent rate than chlorpromazine did.

DH: Akathisia more frequently too.

FA: Oh yes. Unfortunately it had some merit but not enough. And chlorpromazine was so dramatic and universally effective. Fortunately not many people got into escalating doses because hypotension would stop that.

DH: Escalating doses of chlorpromazine?

FA: Yes. Or the marked sedation you got. So it required a great deal of nursing care. These people were unable to walk and were so drowsy. So it kept the dosage down. Nevertheless there were some people, Kinross Wright particularly, who went up to 8 grams.

DA: What did you make of him going up to 8 grams like that?

FA: To me that proved that the only people who can handle such high dosages are schizophrenic. I could make a diagnosis without seeing the patient so to speak. Even though a person has been sick for 30 years they can still be hostile, aggressive, have explosive behavior and be a danger to themselves and others. It is a real challenge. If a person has not responded but has tolerated the drug then you’re justified in going up because we do have, that we didn’t know then, rapid metabolizers who burn up everything while others are slow metabolizers who, even on a low dose, get all kinds of reactions.

DH: So from your point of view you never really got into reserpine the way other people did? Quite a few other people had it a year or so before they had chlorpromazine.

FA: I don’t know exactly how long some of them had it. But it never really took off. Chlorpromazine grabbed everybody and everything and that was it, so CIBA kept reserpine for its cardiovascular uses and that was it.

DH: Who had levomepromazine?
FA: I can’t remember the name of the company. Frankly, the molecule manipulators went to work and by the time of the first CINP meeting in Rome in 1958 I gave a paper on 25 phenothiazine derivatives.

DH: 25!

FA: 25, yes. Some you only tried on a few patients and it was quite clear they weren’t going to work. The interesting thing is that one of them turned out to be excellent as an antipruritic. We ended up knowing that some phenothiazines were predominantly antiemetic, others antipruritic and still others would be antipsychotic.

DH: How did you find out it was antipruritic?

FA: You won’t believe this story. Desperation! I had given it to a number of patients and it was safe. And I had three children with chicken pox driving myself and my wife nuts. Those poor kids were scratching and scratching. So I gave each one of them a 10 mg dose and it worked very nicely. Shortly thereafter I had a patient with bipolar disorder who also had psoriasis; the itching was driving her nuts so I gave her some and it helped. For Compazine (prochlorperazine), it was evident, right off the bat that this was not going to be a very good antipsychotic and I remember vividly a heated meeting with Smith, Kline and French. Nate Kline, Fritz Freyhan and I were there and the whole discussion was what value prochlorperazine going to have in psychiatry. At any rate, it never really did. One of the things that hurt it, were the extrapyramidal symptoms. This was the first non aliphatic phenothiazine which, due to its chemical composition, caused more EPS. It even caused tardive dyskinesia in patients without psychosis who took it for prolonged periods for gastrointestinal problems. But in addition to that the drug got into trouble because they put it out in a suppository form; it was just before we learnt that absorption from the rectum of phenothiazines is very rapid. A large number of children and adults who were given it in suppository form because they were vomiting and could not hold it down, had severe dystonic reactions. In the meantime, Squibb had another phenothiazine that looked like it was going to do very well but unfortunately it caused a fatal agranulocytosis. That was just before they were going to take the data down to the FDA and they decided to hold off. I agreed 100 per cent because it did not represent an advantage over chlorpromazine. It was another aliphatic phenothiazine that went by the wayside. Schering contacted me also. It was shortly after we started working with prochlorperazine, and I did the first study on perphenazine for them. I got Nate Kline, Bert Schiele and some other fellows interested and we presented the first papers on it at a meeting in New York. This drug had a definite advantage over chlorpromazine because it had minimal anticholinergic and cardiovascular effects; it did
not have problems with hypotension, did not cause sedation and was equally effective from an antipsychotic standpoint. We did a lot of work with it at Taylor Manor Hospital in patients with all kinds of problems. Taylor Manor was general hospital psychiatry – it has a geriatric, drug and alcohol abuse, and a children’s section – so we could try it out in these different areas. At the same time we were also looking at trifluoperazine. For the next important thing that happened we have to give credit Charlie Revlon. He was interested in getting into the pharmaceutical business and was buying up Schering stock. The company became aware of this and got concerned that maybe this guy would take them over. So they had to dilute their holdings and spread out. There was a small company called White Laboratories in New Jersey not far from Schering, which made vitamins. Schering had fluphenazine, and White Laboratories were getting their vitamins from Squibb. The Squibb people had been trying to make a long acting antipsychotic and had developed the technique of depot injections. The end result was that Squibb got the rights to make fluphenazine in depot neuroleptic form. White Laboratories were permitted to market it in so called pediatric doses, half mg, quarter mg, 1mg, up to 5mg. Schering went from 5mg on and promoted it as an antipsychotic drug. That became a very big product for them, no question about it. So sometimes it isn’t just science which produces something but a series of coincidences make it possible. It also shows that businessmen can recognize potential advantages in certain areas and can exploit them.

DH: If someone like Charles Revlon could conceivably have taken over a pharmaceutical business like Schering Plough at the time, is this because pharmaceutical companies during the 1950’s were fairly small?

FA: Well, Schering was one of the smallest. It was a German company taken over during the war by the US government. The man who became president of the company was a graduate of Georgetown University, a lawyer, and he was administrator for the government during the war. When the war was over they decided they would not return it to Germany; it became the Schering Corporation USA and he became president of the company. He was a very brilliant guy and a very astute businessman. But the Company it was small and it had no great product. As a matter of fact Smith, Kline & French also was basically a small company except for amphetamines and vitamin preparations.

DH: The thing, people fail to appreciate about the scene during the fifties and even through the sixties is that we assume that these companies have always been big. But they weren’t; investigators were dealing with organizations where you knew all the people.
FA: Yes; for example, when you worked with Merck in those days it was a small company in Pennsylvania. You called up the Medical Director and it would be the same guy you had talked to for the last 10 years. There was not a big turnover of personnel and there were not these mergers.

DH: And they could learn to trust your judgment in a way that now you can’t because the people in charge change every year or two so they don’t know who you are and you don’t know who they are.

FA: You’re absolutely right. It’s a disadvantage for them because they don’t know who to go to for sound research.

DH: It’s also learning. You learn to trust their judgment of people and turn to them, look we’ve got this new problem, what do you make of it?

FA: The other thing that was good about it is that you got to know your pharma colleagues very early on. Len Cook and I were friends within a year after chlorpromazine; I got to know him as a man and learned he was a man of integrity and brilliance. So I felt fairly comfortable with the animal data I got from him.

DH: Right.

FA: That was true for a number of companies. Bud Vane and Claude Strickman had been with Merck for a long time. They both were very good and I got to know them well and meet also their people. Today the turnover is just so rapid that it has become a different ball game. Also, of course, regulations have changed. What a company has to produce to help satisfy the FDA's requirements has made it literally impossible for people like me to be researchers any more.

DH: Because?

FA: Let’s say you’ve got a new drug that you want to have thoroughly worked up, you need electrocardiograms, electroencephalograms, ophthalmological studies and all kinds of biochemical tests. You have to ask patients who are outpatients if they are willing to spend time for which they are not going to get paid. They will be paid in the sense of getting all tests free and medication free but they may get a placebo free. And that’s why things changed. Well, look at the program for this meeting. There are, I guess, a hundred papers of randomized double blind studies with hundreds of patients and they are all multisite. That’s the only way you can do it, and it’s no longer multisite just in the United States. We join up with the Canadians; we join up with the British. I mean there are papers at this meeting were you have action in several different countries around the globe. Now I think something is lost in this process. What is lost is that the men, who are good men, don’t have the opportunity to experience and develop astute clinical observations so that when they see something they recognize it right off the bat. Why can’t they do
that? One, they don’t have enough time; there are all kinds of committee meetings and so on. It’s not like when I was in it. I was in it when I think it was the best time to be in research. There were patients who were desperate; I mean you didn’t have much trouble getting people to agree to participate. We did a certain number of electrocardiograms, EEGs and all these other things but gosh nothing had helped these people before so they were quite willing to participate. It’s more difficult now, much more difficult.

DH: In Europe chlorpromazine was introduced first for acute psychosis. It took them a while to realize it could be used for chronic psychosis as well.

FA: That’s correct.

DH: Did it take a bit of time here or had the coin dropped by that stage here and as a consequence you went straight for the chronic psychoses.

FA: Most investigators did. Unfortunately, that was not always the best thing to do because they were the least responsive patients. They were the patients with acute, early onset psychoses whether schizophrenia, bipolar or affective disorder, the ones who responded. Basically I was in private practice. I had a staff of 10 people working for me and a large number of patients; I would see only acute patients. Chronic patients first of all didn’t have the money for the treatments. A certain percentage of patients we saw were pro bono cases but you can’t run an operation without the income. So I saw acute psychoses with all kinds of etiologies, some clearly in retrospect more organic than functional. But it didn’t matter, these drugs worked when you had acute psychotic behavior whether organic or non organic. Today, a lot of those studies we did are not being done on acute patients; they are done primarily on chronic patients. They are done in so called acute episodes, a relapse kind of situation or a recurrence but that’s not the same thing as acute psychosis.

DH: When did the idea come through that chlorpromazine was antipsychotic; it was introduced first as being useful for a wide range of conditions. It could be used in low doses for mood disorders, when people were anxious, and in higher doses for psychosis. When did the idea that chlorpromazine was an antipsychotic began to crystallize?

FA: It took several years and the reason for that was that what we saw first was alteration in behavior not thinking.

DH: They could still hear the voices but the behavior changed?

FA: That’s right. It took time to realize that certain things were happening. The voices were there but not as intense ad over time they were disappearing, delusions were slowly melting away. This was in the chronic patients. In the acute patients you would have remissions induced by the medication, but you learned that you could not stop the medicine in
the majority of them. For some you could, but for the majority you had to keep the medicine up, which indicated that if they had not continued the medicine they would have become chronic but when you kept it up they were responsive.

DH: Can I ask if you can pinpoint a period of time or a meeting or a group of speakers who began to raise the issue of the drugs inducing negative syndromes; it seems this could have only happened after the dopamine hypothesis was born.

FA: You had the problem that all patients develop a certain tolerance to the sedative effects. They weren’t zombies any more but they were still sedated; you didn’t know whether what you were looking at was apathy related to the illness, which could be the anergia that we call a negative syndrome today, or whether this was drug induced. Now, patients helped us. Some just stopped medicines and the psychosis came back in all its glory. What we learned from these patients is that you could get fairly rapid control of the acute symptoms but that’s all you got. You had to keep plugging away. It was the same experience people had working in the early days with levodopa or with tuberculosis patient and anti-tubercular drugs. It took a while before you made a substantive difference. The other thing that became evident early on too was that for some patients augmentation was necessary and that was evident by the time meprobamate came around. Meprobamate made it possible to treat some patients with antipsychotics because they could be sedated and you didn’t need to give as high a dose of the antipsychotic. Meprobamate could help. It made it possible to reduce the dose of antipsychotic. It might have also produced some anti-extrapyramidal syndrome (EPS) effect. Of course we could do same with phenobarbitone that we did with meprobamate. But the anti-Parkinsonian effect you got wasn’t as dramatic or as consistent as you got with the anti-Parkinsonian drugs but even in those it worked very well. The two that impressed me most were biperiden, which was second as far as I was concerned, and benzotropine was number one. Trihexyphenidyl and other anti-Parkinsonian drugs were too anticholinergic. If you used those with chlorpromazine you’d get severe constipation or urinary retention. Historically we went from the aliphatics, which were predominately sedative, anticholingeric, antimuscarinic and hypotensive drugs to the fluphenazine type medication where you didn’t have much sedation or anticholinergic activity and you could combine the benzotropine and biperiden with the antipsychotic drug with excellent results and very little in the way of undesirable adverse effects.

DH: You mentioned meprobamate. For the modern trainee in psychiatry, from a historical viewpoint, this was a hugely interesting drug which we don’t
have now. We almost don’t have anxiolytics any more. We have the antipsychotics and antidepressants but was there ever anything else? Can you take me through the meprobamate story?

FA: Well, the meprobamate story is an extremely interesting one. Meprobamate came at the right time in that it was quite clear that reserpine was going to be a problem drug and was not going to be suitable for treating non-psychotic patients. Using chlorpromazine in non-psychotic patients, you risked extrapyramidal effects, jaundice, agranulocytosis and dermatological problems. People wondered why take that risk in patients who were not insane. If you were insane, those risks were worth taking. But there were a lot of anxious patients around, lots of them. Meprobamate came along and it worked. It was, at that time, the best anxiety drug we had and, initially, it appeared to have none of the disadvantages of the barbiturates. Later we learned it could become a drug of addiction with issues of abuse and terrible withdrawal symptoms, so it was very hard to wean some patients. That’s true of the benzodiazepines today but that’s getting ahead of the story. My perception was that the company that had meprobamate was accustomed to marketing to the public and whether they did this purposely I don’t know, but there was a shortage immediately of meprobamate. Time Magazine carried pictures of pharmacies with signs in the windows, “Meprobamate due to more people wanting to get it.” Milton Berle called himself Miltown Berle for a while and there were magicians pulling Miltown bottles out of hats instead of rabbits. All of that stuff created an intense interest in this drug, and a lot of animosity. Some of it was generated by the pharmaceutical people because this was a drug that was taking some of their business away. How much of that was true? I don’t know but I have no doubt it was there. Meprobamate did so well that Wyeth marketed its own brand of it as Equanil and did a very good job. There’s no doubt in my mind that at that time it was an advantageous drug to have. If it did nothing else it made you think what does this drug do different from what chlorpromazine or reserpine is doing. By this time we were already looking at other phenothiazine derivatives. It also showed that there are people who are not psychotic but very miserable and are willing to pay good money to get relief. They knew they were never going to end up in institutions, although they often feared that, but they also knew that their condition was impacting on their marriage and social lives as well as their ability to work. A lot of these people we now have categorized as social phobias. In those days we didn’t have social phobias, we didn’t have obsessive compulsives disorder as we now talk about this illness, we didn’t have all these subdivisions of disorders. The disorders were there, but they
weren’t diagnosed as such. There was a need and a market for meprobamate and drugs like meprobamate because, God knows, there was enough overwhelming evidence that the barbiturates were not drugs that you could give out in a cavalier way for a minor condition. People could become habituated to barbiturates in such a short period of time and that is terrible. So you had meprobamate with a very small company in New Jersey first, then Wyeth entered the picture and with its international connections meprobamate became available worldwide very quickly. It made clinicians and researchers begin to ask questions about mode of action, the difference physiologically between the non-psychotic anxious patients versus the anxious psychotic patients. Although meprobamate could help in the psychotic patient, it was not on the psychosis but as an innocuous sedative. That was the difference. The success of meprobamate certainly sparked interest in the search which led to the benzodiazepines. So along comes Librium (chlordiazepoxide), a very interesting drug. I did a lot of the early work and wrote a paper on it which recently Jonathan Cole quoted extensively; he thought it was one of the best descriptions of a drug he had ever read. This was a drug that had a very definite differential between what was a therapeutic dose and one which quickly became toxic. If you got over 50mg - and certainly 75mg in my experience was a dividing point - people became toxic without the benefits. So they very wisely kept the dose down. But it didn’t take long to know that Librium was not going to be another meprobamate and the search was on to look at other analogues of the benzodiazepine series. So next came Valium (diazepam) and that, as you know, became another meprobamate. I mean the demand for Valium was just unbelievable by this time the press had become interested in it.

There were also Congressional hearings those years and I testified for the appropriation that became the foundation of the psychopharmacology unit of the NIH. You also had influential people like Mike Gorman calling attention to all these new drugs and encouraging the formation of patient advocacy organizations that began to put pressure on Congress and the FDA to come up with more of these compounds.

So, meprobamate did very well until Valium came along. By then enough time had elapsed to see meprobamate’s adverse effects and Valium didn’t seem to have them initially. So meprobamate went down and Valium went up. Since then no benzodiazepine after Valium has done as well because, in a sense, they have been “me-too” drugs. They might be a little different in terms of molecular structure but in the clinic they are not as good. Valium is better than Librium and if Librium had been all they came up with the benzodiazepines would have died. As
you know, a lot of efforts have been made to find a replacement for the benzodiazepines but thus far with not too much success. So, we still need them, I mean there’s no question about it, we need this category of drugs. And the minute one is developed the benzodiazepine era will come to an end.

It takes time to get past the glow of the initial benefits and begin to look realistically at what a drug is really doing. I was fortunate. It caused me a lot of anguish to have two patients within a very short period develop jaundice on chlorpromazine. Subsequently I had a patient develop a fatal agranulocytosis. Then I had the poor girl with an acute dystonic reaction that frightened the hell out of the family. I didn’t think they’d ever bring her back to me, but they did. Then the glow begins to wear off and you begin to look at them realistically and ask yourself why these drugs alter behavior and what else they do?

One of the advantages of the old days was that you saw a patient over a period of time. I’m still seeing some patients that I first saw in the late 1950’s and early 60’s.

DH: You do have a perspective that very few people have Frank.

FA: That’s right. I’ve been one for follow-ups. That’s why I could write a paper on the EPS, which took a lot of effort. Just tracking all these people down was difficult. There was the usual problem that they move without forwarding address and so forth.

ECT is still the treatment choice for some patients despite all the drugs we have. Just six weeks ago I got a phone call from a young psychiatrist in Miami who said, “I’m calling you because I’ve got a patient who is depressed and I’ve tried everything under the sun and nothing has worked. Her daughter is saying she should get electric shock and when I asked her why she said, she had it before and it worked so well”. As soon as he told me the woman’s name I remembered her because she was a recurrent depressive who never responded to Elavil or Tofanil in the early days so every time I had to go back to ECT. About ten days ago he called again to say he gave her a course of ECT and she was out of the hospital and home. He told me I gave her a Merry Christmas! Without making an accurate diagnosis you’re probing in the dark. Treatment history and family history are also very important. Blood relatives of some of the patients I had in my study on EPS developed Parkinson’s disease.

DH: Frank, you’ve played a big role in bringing in the antidepressants, Can you tell me that story? Can you take me through your experiences?

FA: Let me tell you first about ECT. I did a lot of ECT in the early days because it was, and is still, the fastest, and when properly administered, the safest treatment. ECT with the technique we use today is now extremely
safe even for very old people. But that was true even in the early days. It wasn’t long after I started ECT that I became friendly with Abe Bennett and he told me what he was doing with succinylcholine so I got into that. I also tried to find an anesthetic to use. I had connections with Squibb and I got Brevital (methohexital) from them. Now, is ECT a good treatment for schizophrenia? Broadly speaking, the answer is no. For certain types of schizophrenia, yes, it is. In depression ECT there is an unknown number of patients who are going to need maintenance ECT. That does have a disadvantage in that you can cause cognitive problems with repeated ECT. It depends, of course, on what kind of current you are using, how frequently and how close together the treatments are. It’s a marvelously effective treatment. But it’s not for everybody.

DH: No.

FA: Some psychiatrists treat young people with ECT but I would not do that myself. Adolescents, yes, because some with severe affective disorders become suicidal and it is the best anti-suicidal treatment because of its rapid action. Now, it’s a shame that the medical and even the psychiatric profession never came to appreciate the real value of ECT. The end result was you had laws passed banning ECT. Texas still has very stringent laws and California still has some. Years ago, medical schools were not doing ECT. It was done primarily in private psychiatric hospitals. ECT did not fit in with the views of the psychoanalysts who controlled practice. I’m not saying that in a derogatory way. It was their orientation in those years and psychoanalysts had no real experience with ECT. When I demonstrated its effect on public television I was called a faker! But all that’s changed. Now medical schools are starting to do ECT.

DH: Who would you give the credit to for turning things around? Max Fink has played a role in that.

FA: There’s no doubt about that. Luther Kalinowsky, Abrams in Chicago and Max Fink have probably been the most influential people on convulsive therapy in the United States. There are new treatments now like transcranial magnetic stimulation (TMS); I just wrote a paper on that with Phil Janicak. So, I’m still active. I don’t do it myself but you don’t need an anesthetic with TMS and that’s a real advantage. The patient is fully conscious throughout the treatment so you’re not having convulsions, dislocations, fractures, confusion or cognitive adverse effects. The patient can get up when the treatment’s over and go out and drive a car with no danger whatsoever. Now it’s never been directly compared with ECT but it should be. It should be done soon because it could very well offer treatment for patients who can’t tolerate drugs, have a physical contraindication, or are unresponsive to drugs. Max Fink is not convinced that TMS
is going to have any real impact on ECT use, but I think it may. People can criticize what I did in the early days, the methodology was not what it should have been, and there were no placebo controlled trials.

DH: Well, TMS is the wave of the future. Let me take you back to the pills and your actual involvement with the antidepressants. I guess iproniazid was first. How did you get involved with that?

FA: I was chief of psychiatry at a general hospital in Baltimore which came under the department of medicine, and the chief of medicine was a tuberculosis specialist. One day he asked me, “Have you ever tried isoniazid?” I asked why and he replied because it does something to tuberculosis patients besides benefit their tuberculosis. Really, I said, what does it do? Oh, he said, it makes them a little more energetic; they’re certainly not as despondent. He didn’t use the word depressed, he said despondent. At that time all we had really was imipramine; we were in the early stages of amitriptyline development. So I said well, this is a well known drug, it’s been around for a while, and we know its hazards. So, I asked some depressed people if they would be willing to take it. There was no doubt it worked, it had some antidepressant effects, however at a price. It didn’t take long to realize that the MAOIs, particularly Marsilid (iproniazid), could cause a number of undesirable side effects that made some people reluctant to use it. But fortunately, it was actually the luck of the draw, in those early days I never had anybody who got jaundice. That’s what really killed the MAOIs in this country. And I never had anybody who had a severe adverse reaction with them. We might had some but we didn’t realize it. I would ask people religiously every time I saw them if they had taken anything since the last visit besides the medication, and did they have any problems? But it wasn’t until I used Nardil (phenelzine) that I began to have problems with dietary things. I also got Marplan (isocarboxazid) from Roche; it didn’t cause the same number of problems as phenelzine but more than I saw with iproniazid. There are people who respond only to one tricyclic antidepressant and not to the others, and there are some who respond only to MAOIs. So there’s a major genetic factor, I think, that accounts for this individual capacity to respond to or be resistant to a particular medication. But we didn’t have too many alternatives.

When you have these people profoundly depressed people who didn’t respond to medication the only thing we had was ECT. There were a lot of people who were very much opposed to it. It was pooh-poohed as a barbarous treatment by some psychiatrists. Of course the movie “One Flew over the Cuckoo’s Nest” didn’t help either. There were some fatalities and, frankly, there were a few people who used it like they were giving
out candy and producing very undesirable consequences. But that’s not
the treatment; it’s the misuse of the treatment that’s at fault. In the same
way I feel that some doctors should be prosecuted rather than criticized
for the drugs they have been prescribing. Inappropriate prescribing is
terrible.

DH: You talked about ECT and MAOIs, what about the tricyclic antidepres-
sants? How did you get involved with Kuhn and Tofranil (imipramine)?

FA: Well, you know about that I think. I know you’ve interviewed Kuhn. I’ve
read what he had to say. I was at that meeting in Zurich where he gave his
first paper on imipramine.

DH: Had you had any hint of this drug before that?

FA: No, it was my first introduction to it.

DH: Right, and there was only a reasonably small group at the talk as I under-
stand it; something like ten or twelve people.

FA: There were so few people there it made me wonder whether we were
going to have a session. We were waiting for it to start.

DH: What was Kuhn like? What did you make of the man?

FA: He came across as an extremely intelligent man with a very sound phi-
losophy. I was very impressed with his attitude towards the ill. He was
very empathetic and compassionate and he had a genuine concern
about helping. But the thing that also impressed me very much was the
astuteness of his observations. He carefully studied each patient that he
gave that drug to. He obviously was convinced of its value. To the point
that you could wonder if he was biased. That crossed my mind but his
integrity was so evident that you were willing to say that he’s at least not
willingly biased and he’s trying to present the facts as best he can. The
other disadvantage was the small number of patients in the study; I don’t
think he had even 50. I don’t know the exact number but it was very
small and the period of observation was relatively short, but his descrip-
tion of what happened to those patients, I will never forget. I have often
compared his paper to Lincoln’s Gettysburg Address; it’s short, succinct
and he’s got all the facts right there. You can’t misunderstand what he’s
saying if you’re reading it carefully. So I was very impressed and sub-
sequently I went back and spent some time with him as he probably
told you. I met him at other meetings and then I brought him in 1970
to Baltimore for the “Discoveries in Biological Psychiatry” meeting I put
together with Barry Blackwell. At any rate, that was my first introd-
cution to the drug. Initially, because of hope that this was going to work,
risks were taken. We didn’t know some of the potential adverse effects,
the cardiovascular ones particularly. Every patient I gave imipramine to I
kept a very detailed record on. At another World Congress of Psychiatry
in Montreal I gave a paper on patients treated with imipramine continuously for one year and that was the first paper of that type I knew of in my field. There was no doubt that imipramine worked, and there was no doubt that it had some unpleasant anticholinergic effects like blurring of vision, dryness of the mouth. Most patients hated that and you could get urinary retention in men who had a prostate problem. Working with imipramine also drove home another point which I learned very quickly with chlorpromazine. You’re not treating an illness but a human being who has an illness and you’ve got to look at it from that viewpoint. I wrote a paper very early and in those days getting a new drug paper published was difficult because there was a certain amount of skepticism about all these drugs. My first paper on imipramine, which described what a clinician saw, was published in my medical school’s journal which went out to maybe a thousand doctors. Now Elavil (amitriptyline) took advantage of the fact that imipramine broke the ground. Amitriptyline had some very distinct advantages over imipramine; it was a little bit more sedative and therefore the anxious depressed patient benefited. Imipramine tended to make some people a little bit more anxious. So that was the first thing that really showed up with amitriptyline.

DH: How did you get involved with the clinical work on that?
FA: I’d done some work for Merck in other areas and so they called me up. I went there together with Nate Kline, Doug Goldman and Fritz Freyhan; we were the people they contacted because we were willing to look at drugs. Initially, the thinking was that in animals’ amitriptyline resembled chlorpromazine so much that it was going to be an antipsychotic. Well, it didn’t take long to prove that it wasn’t. It was clear that, pretty much as Kuhn observed, patients who responded were depressed, so I took that position and Merck bought it.

DH: Merck also bought 50,000 copies of your wonderful book, Recognizing the Depressed Patient because they felt people needed to be educated as to the nature of the syndrome. This is a tricky one isn’t it? Obviously if you’ve got a new treatment, if you’re opening up a new market, people do need to be educated. Trying to draw the line so as to just how much they should be educated is difficult.

FA: Let me clarify the picture with the facts. The book was written. It was not paid for by Merck. They had not funded it. I wrote it on my own. It was after a review appeared in JAMA; a very favorable review, that Merck came and said we would like to buy 50,000 copies of the book. Now I wrote that book because I was absolutely convinced that the people who saw depressed patients first were family doctors. And they wanted to get this out to the family doctor because until then their marketing of
amitriptyline was to the psychiatrists. As far as I was concerned they were going to help me to achieve the goal I had when I wrote the book. So I said yes. It worked. The book was very well received but I don’t know how much of an impact that had on the actual sales. A recent theory is that it took a long time for family doctors to be convinced.

DH: Is that because during the 1960s and ‘70s they thought that the nervousness they saw was more of a state of anxiety to be treated with minor tranquilizers?

FA: Yes. As a matter of fact as you know Will Sargant made a very important point in a lead article in the BMJ back in the late 1950s or early ‘60s: “If you think he’s anxious give him an antidepressant”. Basically, that was his point. Family doctors or non-psychiatrists whether they are internists, general practitioners or gynecologists would call these people anxious but not depressed. And that’s still true today unfortunately.

DH: You were involved in the early days of CINP, which as I understand it, was largely perceived in America as being a very European organization.

FA: Very few people over here knew about the CINP at all. When I brought it up at our first meeting in New York, that we should start a College here, it was based on my experience with being at the founding of CINP in Milan. And, there was a need for this College. Psychiatrists were not talking to pharmacologists. Pharmacologists were not talking to psychiatrists; nor were the biologists or geneticists. It was clear that this was a very complex situation and it would be helpful for all of us if we could talk to each other. So, when Ted Rothman approached me about such a meeting I quickly jumped in with some ideas and he invited me to the meeting and in the course of the discussion I brought up what had happened in Milan and said, you know, we really should have an American College. It took some time to work out how it should be formed but it’s a reality today and it’s become, in my judgment, the most prestigious organization of its kind in the world. I’m very proud to have had a role in its beginning and it has made a world of difference when you look at what goes on at these meetings today with the basic scientists and psychiatrists talking to each other, exchanging views. That’s for their benefit but also for the benefit of patients.

DH: You’re saying the first meeting about the idea of some kind of society was Ted Rothman’s?

FA: Ted had an idea there should be something. He wasn’t quite clear what it ought to be. His idea was that he was going to get together about a dozen of us in New York, and the reason for that was that the medical director from Geigy, who was going to fund this thing, would be at the meeting and he was in New York. By this time, Jonathan Cole was in
Boston, I was in Baltimore, and Bernie Brodie was in Washington so we were all fairly close together. The only one who really had to travel any distance was Ted Rothman. Leo Hollister was not there initially but he came in later, so the bulk of us were from New York.

DH: So it was an East coast thing at the start?
FA: Basically, yes. There were a few others, I don’t remember them all. Joe Tobin came, he was from Wisconsin. So there were some who came a distance to get to the meetings. From the very beginning, Bernard Brodie, a basic scientist, was also there. We also had Joe Brady a psychologist. So almost from the beginning there was good representation from different specialties.

DH: The early meetings were held in New York on the East Coast. Why did you ever think to move to Puerto Rico?
FA: A snowstorm.
DH: Really?
FA: Oh, yes. I think it was 1963, I know I came from Rome for the meeting. Milt Greenblatt was the president that year and the meeting was in Washington. We had a terrible blizzard and only a limited number of people attended. I don’t think a hundred people showed up for that meeting. This led to a discussion about finding a better place to meet. They didn’t want to come to Florida, so the decision was to hold it in Puerto Rico. As you would expect, there was some dissatisfaction with that, so then we moved back into the United States and we had meetings in New Orleans, Las Vegas and Palm Springs. We also met in Hawaii on several occasions and today we’re back in San Juan.

DH: The early meetings, as I understand it, were very informal brainstorming sessions.
FA: Exactly.
DH: It’s a lot more structured now isn’t it?
FA: Yes, it has to be.
DH: Well, yes, possibly it has to be.
FA: It has to be. You’ve got a much greater number of members and a number of invited guests. We have more people from outside the United States here than we had at those first meetings. That’s a change. Tomorrow, the first of poster sessions, there are 161 posters. We didn’t have that many presentations in a whole meeting in the beginning. In fact, we didn’t have poster sessions. We had morning sessions. The afternoons were to lie around on the beach and to have brainstorming sessions. It was great, because it really gave us a chance to get to know each other. Even the evening sessions were finished early so we could go out to dinner together. In those days, in the beginning, the pharmaceutical company
presence was there but not felt. Not that I’m against their involvement. I’m grateful that the industry made some of these things possible. It wouldn’t have happened otherwise. Then, unfortunately, the College got accused of being an elite old boys club because people couldn’t get in. I raised that issue this morning at the History Meeting because that’s being alleged again, that we’ve not taken in people who really are qualified. It’s a question of a reluctance to increase the membership and I can understand that, but I think we’ll have to, in another couple of years, increase the number of members.

DH: Do you think the membership shifted much towards the basic sciences, from your point of view?

FA: Emphatically, yes, and that has discouraged a good number of people to attend. They’re not interested in many of these topics. They would much rather be able to go back and say I learned something that I can use in my practice, or that I can use in my teaching of the residents. I frequently have people talk to me about this who I don’t think would have talked to me, otherwise, but they know I have been involved and dedicated to this college. We have some very fine young people here at this meeting but they’re not getting involved as much as I think they should be in the leadership for the future…

DH: Leadership for the future?

FA: Yes.

DH: On this note we conclude this interview with Frank Ayd. Thank you.
THOMAS A. BAN

Interviewed by William E. Bunney Jr.
Boca Raton, Florida, December 10, 2007

WB: I’m William Bunney and I’m interviewing Dr. Thomas Ban. It is December 10, 2007. We are at the annual meeting of ACNP in Boca Raton. Tom, could you begin by telling us something about your background, early interests and how did you get started in medicine?

TB: I was born in 1929 in Budapest, Hungary in a middle class family. As far as I can remember I was interested in books and in my teens I was a voracious reader, wrote poems, short stories and even a book. At age sixteen, I won a student competition award for an essay on the transformation of the 19th century novel in the early 20th century; I attributed it to the influence of Freud and psychoanalysis. I was encouraged to prepare for a career in literature. But, my world that had collapsed with World War II was changing again. Hungary became a “people’s democracy”, and I thought it would be safer to enter medical school.

WB: What about college?
TB: We went straight to university from high school, but I had the equivalent of a college education by auditing courses in history and philosophy.

WB: Where did you go to university?
TB: The Medical School in Budapest, in 1948. It was the old Semmelweis Medical University, only the name had changed.

WB: When did you get your medical degree?
TB: In 1954.

WB: Did you do any research during the time you were in medical school?
TB: No, but in the fourth year, with a classmate of mine, we received First Prize for our essay on Post-traumatic epilepsy. It was also during that year I became interested in psychiatry. I was fascinated by the lectures of Gyula Nyiro, our professor. He was a structural psychopathologist who viewed mental symptoms as abnormalities in the processing of signals between and across different levels of three mental structures corresponding with the three neuronal component of the reflex.

WB: When you got out of medical school, what did you do?
TB: I got a job as a junior physician at the National Institute of Nervous and Mental Diseases.

WB: What about residency?
TB: We did not have residency training. I started on one of the services of the Institute where patients with “neuroses,” called anxiety disorders today, were treated.

WB: How were they treated?
TB: Most of them were given tonics, like Arsotonin and Strychnotonin by daily subcutaneous injection. We did psychotherapy, quite frequently with chemically-induced abreactions, and hypnosis in some patients.

WB: How long were you on that service?

TB: For six months. Then, I was assigned to one of the admission services at the Institute.

WB: What kind of treatments did you have there?

TB: We had a morphine-scopolamine combination for controlling agitated and violent patients, and a phenobarbital and bromide combination, BromSevenal, for sedation. We also used paraldehyde and chloral hydrate. We treated schizophrenia with insulin coma, depression with tincture of opiate, and both with ECT. Then, sometime in the spring of 1955, we had our first patients on chlorpromazine and reserpine. We also had a couple of patients on lithium.

WB: You used lithium in the mid-1950s?

TB: Yes, in 1955. György Sándor, my service chief followed the literature very closely. I remember having our lithium supply prepared in the pharmacy and the Institute had a flame photometer to monitor plasma levels.

WB: Did he publish?

TB: Dr. Sándor was not interested in writing papers, but, to my surprise, he was open to my suggestion, when the new drugs appeared, to start a quarterly Digest for the Institute to keep everyone abreast of developments.

WB: Did you publish any papers in Hungary?

TB: I published three brief reviews. One was on the development of the diagnostic concept of neurosis, another on the story of “BromSevenal,” and the third was an overview of the history of psychiatric nursing.

WB: It seems that you got your first experience with the new drugs in Hungary?

TB: I had my first exposure to some of the new drugs.

WB: Did you use Marsilid (iproniazid) in Hungary?

TB: Marsilid was used only at our special service for tubercular patients.

WB: Was it used in depression?

TB: No, it was only used in the treatment of tuberculosis.

WB: When did you leave Hungary?

TB: In November 1956, after the revolution.

WB: You went to Montreal?

TB: Before Montreal I spent a few weeks in Vienna at the University Clinic of Hans Hoff. I started with my fellowship at the Montreal Neurological Institute (MNI) in early January 1957.

WB: How did you get that fellowship?

TB: I wrote to Wilder Penfield, and told him about my essay on post-traumatic epilepsy. I also told him that I would like to further my training in his
Institute. I was familiar with the monograph he wrote with Herbert Jasper on Temporal Lobe Epilepsy and the Functional Anatomy of the Brain from editing our Digest. I did not expect he would respond, but he did, and even contacted the Canadian authorities to issue me an immigrant visa. In less than two months after I crossed the Hungarian-Austrian border, I was attending Francis McNaughton’s epilepsy clinics, and Herbert Jasper’s research rounds at the MNI. In June 1957, I left for Halifax to do a rotating internship at the Victoria General Hospital of Dalhousie University. A year later I passed the Canadian Medical Council examinations which allowed me to apply for a license to practice medicine.

WB: How did you get to work with Dr. Lehmann?
TB: I was accepted in McGill’s residency training program and was assigned for my first year to the Verdun Protestant Hospital (VPH,) a large psychiatric hospital affiliated with McGill that served the English speaking population of the city, where Dr. Lehmann was clinical director. I met Dr. Lehmann for the first time on the 1st of July 1958, and, a few days later, I started to work with him on some of his research projects.

WB: How did this happen?
TB: Doctor Lehmann asked whether any of us new residents would be interested to work with him on some of his projects.

WB: How many of you were interested?
TB: From the six of us, only me. But later on some of the others got on board.

WB: What was your first project?
TB: I got involved with several projects simultaneously. In one, my task was simply to stay with some of my fellow residents and other psychiatrists who were given psilocybin.

WB: Psilocybin?
TB: At that time it was thought educational for those dealing with psychotic patients to get an idea about what patients were experiencing.

WB: What about the other projects?
TB: In another project, we studied the effects of prototype CNS acting drugs, like dextroamphetamine, secobarbital, chlorpromazine, prochlorperazine, imipramine, and lysergic acid on enzyme functions and on biological systems of low complexity, including urease, firefly lantern extracts, proteus bacteria, oat seedlings, the feeding reflex of hydra and dandelion sleep movements. And, in a third, we studied the effects of phencyclidine (Sernyl), in different doses and in different diagnoses, as well as in a few normal subjects. Dr. Lehmann received a supply of Sernyl from Parke-Davis to find out whether it would be suitable for the facilitation of psychotherapy. It was not, but I became interested in the compound and it did not take me long to recognize it was a substance that could change
how one experienced oneself and the world. Its effects were distinctly different from psilocybin. Just from curiosity I also gave Sernyl with a friend to a few rats. To our amusement, the animals started to walk backward!

WB: Did you publish your findings?

WB: We had two papers on Sernyl: one, in 1961 in the Canadian Psychiatric Association Journal, and another, few years later, in the proceedings of the fourth CINP Congress. My first paper on Sernyl, and my first paper based on my conditioning research appeared almost simultaneously. They were really my first “scientific” publications.

WB: How did you get involved in conditioning?

TB: At the time I started my residency at McGill we were still expected to prepare a thesis, based on some research, but mainly a literature review, to get our diploma in psychiatry. Since VPH had a conditioning laboratory, Dr. Lehmann, who was also my thesis supervisor, encouraged me to select a topic related to conditioning.

WB: When did you get your Diploma from McGill?

TB: In 1960, and I got it with distinction. Furthermore, on the recommendation of my examiners, my thesis was published with some modifications under the title, Conditioning and Psychiatry, by Aldine in the United States in 1964, and by Unwin in the United Kingdom, in 1965. I had a Forward written by Horsley Gantt, the American disciple of Pavlov. Dr. Gantt apparently liked my thesis, and invited me to join his Society, the Pavlovian Society of North America. A few years later, in 1966, at the World Congress of Psychiatry in Madrid, I also became one of the founders of the Collegium Internationale Activitatis Nervosae Superiors (CIANS,) an international society of people involved in conditioning research.

WB: Does that College still exist?

TB: Yes, but after Dr Gantt died it was no longer the same College.

WB: When did he die?

TB: In 1980. He got seriously ill just a few weeks before a CIANS Congress in Milan and passed away soon after.

WB: Would you like to say something about your research in conditioning?

TB: From reviewing the literature I got the idea that behavioral CR variables might provide a bridge between psychopathology and neurophysiology. So, as soon as the thesis was completed, I developed a diagnostic test procedure based on the conditioning method using the eyelid closure technique. Then, in the 1960s, in collaboration with Drs. Lehmann and Bishan Saxena, a psychologist, we developed a conditioning test battery, the Verdun Conditioning Test Battery (VCTB) using several techniques to study psychopathological mechanisms and psychopharmacological effects. We also developed, in the 1960’s, a psychometric test battery,
the Verdun Psychometric Test Battery (VPTB) that included several perceptual, psychomotor and other tests. Our interest was identifying predictors of treatment response to psychotropic drugs with the employment of these batteries. In the early 1970s we published our findings in a monograph; Experimental Approaches to Psychiatric Diagnosis. Although I did not continue with research in conditioning after the mid-1970s, all through the years I have been thinking of resuming it. To acquire a conditioned reflex (CR) is an innate property of the brain and our studies had indicated that CR variables, like acquisition, extinction, differentiation, reversal, etc., might provide a key to the understanding of the pathophysiology of abnormal mental functioning.

WB: What did you do after your residency?

TB: My residency was cut short because I was promoted from the first to fourth year and in 1959 I became the junior member of Cameron’s research team on “psychic driving”. Ewen Cameron was chairman of psychiatry at McGill. He was one of the Nuremberg-psychiatrists and a past president of the American Psychiatric Association (APA).

WB: Would you like to say something about the research?

TB: The idea behind Cameron’s research was that by wiping out all memories one would also wipe out pathological patterns in the brain, and one might be able to rebuild the psyche anew. We also explored the possibility that it might be sufficient just to disorganize memories. For wiping out memories we used regressive ECT, which Cameron referred to as “de-patterning”; for disorganizing memories, we used psychomimetic drugs and sensory isolation, and for rebuilding, repetition of verbal signal therapy which he referred to as “psychic driving.” As the junior member of the team I had to do whatever needed to be done, but my specific responsibility was the monitoring of changes in psychophysiological measures and CR variables. Today, what we did, might sound rather unsophisticated but it corresponded with the kind of research people did in those years. In our “sleep room” for example, where most of the research was done, in one bed a patient was treated by our team with regressive ECT, and in the next bed a patient was treated with “anaclitic therapy” by another research team, in which, grown ups were mothered like babies. For me, still pretty much a foreigner in this new world, both treatments were rather strange, but the rational for our experiment was at least as sound as the treatment used by the psychoanalytic group. In fact, we learned from our experiments that some patients with schizophrenia were not affected by sensory isolation, and also that wiped out obsessive-compulsive patterns re-emerge much sooner than memory returns. I left the team before it became public that the grant supporting our project came from the Society for Investigation
of Human Ecology, a cover organization for the CIA. Cameron was vilified by the press, resigned and died shortly after, while mountain climbing. It was never completely clear whether he knew some of the money was from the CIA. I certainly did not. But even if he had known, I don’t think he would have cared. Funds from the CIA were just as good as funds from anywhere else. He was interested in what he was doing and dedicated to help his patients.

WB: When did you get involved in drug studies?
TB: In the late 1950’s. And, then, in the early 1960’s Jon Cole suggested Dr. Lehmann to apply for a grant that would support an early clinical drug evaluation unit (ECDEU) at VPH, which, by that time was renamed, Douglas Hospital (DH). Lehmann was hesitant to pursue the matter, but when I expressed interest and willingness to direct the unit, we applied and our unit became one of the first in the program. So, during the 1960s and 1970s, we studied virtually all the psychotropic drugs that became available for clinical use in Canada and United States, and many others that never made it. I was told by Bill Guy, who was analyzing our data at the Biometric Laboratory of George Washington University, that we studied two or three times as many drugs as the other units in the program.

WB: Which were the drugs you studied?
TB: I think, cyclopentimine, a sympathomimetic alkylamine, and RP 8228, a phenylpiperidyl acetoxymethane, were the first drugs we published on.

WB: This was in the early 1960’s?
TB: We studied these drugs in the late 1950’s before we set up our early clinical drug evaluation unit and published our findings in the early 1960’s. When I first became involved with clinical investigations, it was a commonly held belief that inducing extrapyramidal signs (EPS) was a prerequisite for responding to neuroleptics. The newer neuroleptics induced more frequent and severe EPS, but contrary to the mainstream, in our hands none of the newer drugs was any better than chlorpromazine. In fact, chlorpromazine appeared to be a more reliable treatment than any of its competitors. We conducted studies with “incisive neuroleptics,” like prochlorperazine and thioproperazine, which were more potent on mg per kg basis in inducing both therapeutic effects and EPS, and also with “sedative neuroleptics,” like methotrimeprazine, referred to as levomepromazine and chlorprothixene. Our findings with these drugs did not change our impression; “incisive neuroleptics” did not offer any real advantage over “sedative neuroleptics.” There were differences in adverse effects, but not in therapeutic effects. In our conditioning studies the effect of neuroleptics on the extinction of the orienting reflex, seemed to be a more reliable predictor of whether a neuroleptic would work than the appearance of EPS.
WB: What about your findings with antidepressants?

TB: We were among the first to report on clinical findings with desipramine, the demethylated metabolite of imipramine, the first selective norepinephrine (NE) inhibitor. In our study desipramine did not seem to be a better antidepressant than imipramine or amitriptyline, the two antidepressants available at the time. So we were somewhat puzzled when, a few years later, the catecholamine hypothesis of affective disorder was formulated. If the hypothesis was correct, desipramine should have been better than imipramine, the parent substance that had an effect on both 5HT and NE re-uptake. We were also involved in the early 1960’s in studying trimipramine, a tricycle compound which has no effect either on NE or 5-HT reuptake. It was just as good an antidepressant as any of the NE and/or 5-HT uptake inhibitors. Again, we were contrary to the mainstream. Those were exciting times, learning about these new drugs. We studied sevarla tricyclic antidepressants; amitriptyline was more sedative than imipramine; desipramine had less anticholinergic side effects; trimipramine could safely be administered in combination with monoamine oxidase inhibitors; doxepin did not cause cardiac death in overdose, etc.

WB: You didn’t have rating scales at the time?

TB: We used two scales from the very beginning, the Verdun Target Symptom Rating Scale and the Verdun Depression Scale, developed by Dr. Lehmann in collaboration with Charlie Cahn and Roger deVerteuille for the first North American study of imipramine. We also used a comprehensive Psychopathological Symptom Check List (PSCL.) But, for me, changes in the psychopathological symptom profile of individual patients were far more informative than changes in rating scale scores. In the early 1980’s, to get more information than from conventional scales, like the Brief Psychiatric Rating Scale and Hamilton Depression Scale, we (in collaboration with Bill Guy) translated the AMDP and AGP Systems Manuals for the Assessment and Documentation of Psychopathology that were used in German speaking countries. At the same time, with a group of Italian psychiatrists in Pisa, we updated the ECDEU Assessment Manual, a collection of rating scales for use in clinical investigations, prepared by Guy and Bonato in 1970.

WB: You were involved in the clinical development of how many psychotropic drugs?

TB: Probably about 90. It would be difficult to recall by name all the drugs we studied. The list includes benzquinamide, butaclamol, butaperazine, clobazam, clomacran, clomipramine, clovoxamine, fluspirilene, flutroline, maprotiline, mesoridazine, mianserine, molindone, nomifensine, pimozide, propericiazine, viloxazine, and many others.
WB: Any observations or findings you would like to share?
TB: We noted carbamazepine’s effect on mood in the mid 1960’s while studying it in epileptics; we had shown that nylidrine potentiates the effect of phenothiazines; we recognized the potential use of metronidazole in the treatment of alcoholism, of propranolol in organic agitation, and of naltrexone in controlling hallucinations in chronic schizophrenia; and we replicated Art Prange’s findings with TRH in depression. In the late 1960’s and early 1970’s we explored the possibility with Dr. V.A. Kral of using a pharmacological load test, such as 5% carbon dioxide inhalation, and intravenous injection of methamphetamine or sodium amobarbital in the prediction of therapeutic response in elderly patients to prototype psychotropic drugs, like methylphenidate, meprobamate, amitriptyline, thioridazine, nicotinic acid and fluoxymesterone. We had numerous statistically significant findings but none of them was of clinical significance.

WB: So, you had a special project in psychogeriatrics.
TB: We had an NIMH grant to study psychotropic drugs in the aged while I was with McGill and I continued with clinical investigations in the elderly during the Vanderbilt years. We were among the first in the 1980’s to report favorable effects with nimodipine, a calcium channel blocker and choline alfoscerate, a cholinomimetic substance in old age dementias. We had done several studies with Ateroid (glycosaminoglycan polysulfate), a substance with heparinoid activity and I noted that it helped some patients with Alzheimer’s and also some patients with vascular dementia.

WB: Did you publish all these findings?
TB: We presented and published most of our findings. In the early 1960’s together with a few colleagues interested in clinical investigations with psychotropic drugs in the Province of Quebec, we founded, the Quebec Psychopharmacological Research Association (QPRA), the predecessor of the Canadian College of Neuropsychopharmacology that provided a forum to discuss research findings. The proceedings of most of the QPRA symposia were published and made available. It was at a QPRA symposium where we presented our findings in the first North American studies with haloperidol and triperidol. And it was also at a QPRA symposium where we presented our findings in the first North American studies with chlorprothixene and clopenthixol. We were involved in the early years in side effect reporting to both the Canadian Health Protection Branch and the FDA. We thought that communicating some of the side effects we encountered was sufficiently important that we organized a QPRA symposium dedicated to skin pigmentation and ophthalmological changes seen in patients treated with high doses of chlorpromazine over a long period of time. Another QPRA symposium dealt with thioridazine-induced
cardiac conductance changes. Our EKG studies with thioridazine were triggered by a report on two fatalities in the Canadian Medical Association Journal in 1963, and our findings reported in 1964 in the same journal indicated that thioridazine produces a dose dependent prolongation of the QT interval that could lead to ventricular fibrillation. It might be relevant for the historical record that on the request of Sandoz, the Swiss drug company that manufactured thioridazine, we invited M.H Wendkos, a cardiologist at the Coatesville Veterans Administration Hospital in the United States to our QPRA symposium, and he argued that the EKG changes with thioridazine were due to “benign repolarization disturbances”.

WB: You worked with Heinz Lehmann until when?
TB: From 1958 to 1976 while I was in Montreal but our collaboration continued after I went to Nashville. I started as his resident, then I became his Co-Principal Investigator, and when I was appointed Director of McGill’s Division of Psychopharmacology, he chaired our Board of Advisors. I think it was on his recommendation that I was asked to coordinate the Canadian Mental Health Association’s (CMHA) studies on Nicotinic Acid in the Treatment of Schizophrenia.

WB: Would you like to say something about those studies?
TB: It was a series of collaborative studies designed to replicate Abe Hoffer’s findings. But, as you probably know, we could not. Niacin was just not effective in the treatment of schizophrenia, regardless of whether it was given alone or in combination with ascorbic acid or pyridoxine. There was no indication in our studies that niacin would augment the effect of neuroleptics either in acute or in chronic schizophrenic patients. We did not have a single patient who markedly benefited. To stop the nicotinic acid craze, which affected psychiatry in Canada more than any other country because Hoffer practiced in Saskatoon, our findings were widely publicized. They also found their place in the American Psychiatric Association’s Task Force Report on Megavitamin Treatment in Psychiatry. I was a member of that Task Force; Morrie Lipton, a distinguished past president of ACNP, was chairman.

WB: You mentioned McGill’s Division of Psychopharmacology. When was that established?
TB: In 1971. It was the first Division of Psychopharmacology in a University Department of Psychiatry. It started as a network of clinical investigators in seven McGill affiliated hospitals.

WB: So, we are now in the 1970s?
TB: Yes. Just about the time that the Division was established I became Head of the Canadian Reference Center of the International Reference Center Network on Psychotropic Drugs. The Network was a joint effort
between the Division of Mental Health of WHO and NIMH, and it was coordinated by Alice Leeds from Washington. It was also the time, or might be a little bit later, that we started WHO’s first training program for teachers of psychopharmacology. It was initiated by Gaston Castellanos, an officer in WHO’s Division of Mental Health. We had several Fellows in that program annually from the early 1970’s to the late 1980’s. The first group of four Fellows was from Latin America: Ronaldo Ucha Udabe, from Argentina, Luis Vergara from Panama, Carlos Zoch from Costa Rica, and Luis Galvan from Mexico. They were followed by Torres-Ruiz from Mexico and Imaz from Argentina. I had Jüri Saarma, one of Kraepelin’s successors as Chair of the Department of Psychiatry at the University of Tartu in Estonia, working with me for about a year with the Fellows. Soon after I moved to Nashville, the program moved with me and we had three Fellows, one after the other, from Czechoslovakia. Two of them, Jan Liebiger, and Eva Ceskova were to become professors of psychiatry, heads of university departments, after returning home, and one, Václav Filip, was to set up the first Clinical Research Organization (CRO) in that region. Then, we had Asano and Higano from Japan, Rudra Prakash from India and Aitor Castillo from Peru. Among the last Fellows I had were Marek Jarema and François Ferrero. Marek was to become head and professor of one of the three psychiatric university clinics in Warsaw, and François was to become head and professor of the Department of Psychiatry at the University of Geneva.

WB: Could you say something about your WHO program? What did the Fellows do?

TB: They participated in our activities and got experience in designing and conducting clinical drug studies, processing and analyzing data, and preparing reports.

WB: Did you keep contact with your Fellows after they left?

TB: I did, and developed research collaboration with most of them. In the late 1990’s we registered a research-company for the clinical profiling of psychotropic drugs.

WB: When did you move to Vanderbilt?

TB: In 1976.

WB: What was your position at Vanderbilt?

TB: I went there as director of the clinical research division of the Tennessee Neuropsychiatric Institute, a research facility on the premises of an old state hospital. Then, when the Institute was declared a fire hazard and closed, I continued at Vanderbilt as a tenured professor in the Department of Psychiatry until becoming emeritus in the mid-1990s. From the
Vanderbilt period I spent two years, from 1981 to 1983, on an extended sabbatical in Geneva.

WB: What did you do in Geneva?
TB: I was consultant in psychopharmacology to the Division of Mental Health of WHO. During my first year we carried out a “consensus study” among opinion leaders to find out their agreement how to use psychotropic drugs. So, we asked 28 opinion leaders with representation from five continents whether they agreed or disagreed with 32 treatment-related statements. We got a 100 percent consensus in response to four statements only. All OLs agreed that neuroleptics are indicated in the manic phase of manic-depressive psychosis; that long acting, depot neuroleptics should be used in the maintenance therapy of chronic schizophrenic patients who are unreliable about taking their medication; that amitriptyline has sedative effects, and that intravenous benzodiazepines are the treatment of choice for controlling status epilepticus. After returning to Nashville I remained involved in consensus research with Mitch Balter and Uhli Uhlenhuth, until Mitch’s untimely death. Another project I initiated at WHO was the development of an international network of clinical investigators, or more correctly a network of clinical research units, for the study of psychotropic drugs. My idea was to create a self-supportive network from contracts with the drug industry for efficacy studies on new drugs which would develop and implement a methodology for the clinical profiling of psychotropic drugs. Norman Sartorius seemed pleased with the idea of setting up the network, and Sandoz, was ready to sign our first contract. Bissy Odejide, one of my former WHO fellows, at the time a professor of psychiatry at the University of Ibadan, Nigeria, agreed to direct the new program with me as consultant, and in a whirlwind trip, I traveled around the world from Cairo to Tokyo and Buenos Aires to identify prospective lead investigators in the network. By the time I returned to Geneva, the project was dropped; I never learned who blocked the project. It would have provided for worldwide clinical development of psychotropic drugs, a data base that could have prevented confounding marketing with education about psychotropic drugs, and it might have generated feedback for pre-clinical research on developing rational treatments.

WB: Was there a central theme throughout your lifetime of research?
TB: The central theme of my research shifted during the years, from trying to find a common language for the pharmacodynamic action of psychotropic drugs and mental pathology, to trying to identify pharmacologically homogeneous populations within psychiatric diagnoses. The turning point was the publication of my text, *Psychopharmacology*.

WB: When was it published?
TB: It was published in 1969 by Williams and Wilkins. I think it was the first book in which psychopharmacology was presented as a discipline and not just therapy with psychotropic drugs. It was probably also the first book in which the development of psychotropic drugs is systematically reviewed from structure-activity relationships to clinical applications. The first part, General Psychopharmacology, is based on the material discussed at an ACNP Workshop, *What Preclinical Information Does the Clinician Expect to Be Given Prior to Conducting a Clinical Trial*, for which I tabulated all the information ie brochures we received on the drug before starting a study with their drugs; the second part, Systematic Psychopharmacology, is based on a series of papers, published in Applied Therapeutics, in which all the information I was able to access about different groups of drugs, e.g., phenothiazines, benzodiazepines, in clinical use are reviewed; and the third, Applied Psychopharmacology, on the notes I used in teaching pharmacotherapy to psychiatric residents a McGill. It was in the Closing Remarks of *Psychopharmacology* that I first recognized the need to resolve the pharmacological heterogeneity within the diagnostic groups for neuropsychopharmacology to progress.

WB: How did you go about it?
TB: First I thought that one might replace old diagnostic presuppositions by new diagnostic concepts, built from new building blocks, based exclusively on biologic criteria. But, by the mid-1980’s, I recognized that biological measures have not shown to be anything more than epiphenomena of mental illness, and pharmacokinetic differences contributed little to the differential effect of psychotropic drugs. So, in a paper published in 1987, I postulated that there is a clinical prerequisite for neuropsychopharmacological research; that the meaningfulness of biological, including psychopharmacological findings, depends upon whether they can be linked to a prior, valid diagnostic category based on psychopathology and psychiatric nosology.

WB: How did you get to this?
TB: I came across a paper by Frank Fish, a British professor of psychiatry published in 1964 in Encephale, a French medical journal, in which, by re-classifying patients with schizophrenia using the method of Karl Leonhard, a German professor of psychiatry, he found a moderate to marked response to neuroleptics in more than 4 in 5 patients diagnosed as “affect-laden paraphrenia,” - a sub-population of “unsystematic schizophrenia,” characterized by delusions with intense emotional participation – and in less than 1 in 4 patients diagnosed as “systematic hebephrenia,” a subpopulation of “systematic schizophrenia”. Stimulated by Fish’s findings we developed several instruments for
identifying treatment responsive sub-populations that might be covered up by consensus-based diagnoses. These instruments include, A Guide to Leonhard’s Classification of Chronic Schizophrenias (GUIDE), the DCR (Diagnostic Criteria for Research) Budapest- Nashville for the Diagnosis and Classification of Functional Psychoses, an instrument created in collaboration with Bertalan Pethö’s Hungarian team; CODE-DD Composite Diagnostic Evaluation of Depressive Disorders; and CODE-HD Composite Diagnostic Evaluation of Hyperthymic Disorders, developed in collaboration with Peter Gaszner, a Hungarian professor of psychiatry, while he was working with me in Nashville. CODE-DD, the prototype of the CODE System, was adopted and translated from English into Estonian, French, Hungarian, Italian, Polish, Portuguese and Spanish.

WB: Would you like to say something about your findings?

TB: Our findings with the GUIDE and the DCR showed that the significantly different therapeutic response to neuroleptics in the two classes of schizophrenia reported by Fish, and also by Christian Astrup, is not restricted to therapeutic effects but applies also to adverse reactions. In an analysis of our international survey of about 800 chronic hospitalized schizophrenic patients, we found that tardive dyskinesia (TD) occurred more than three times as frequently in patients diagnosed, “systematic schizophrenia,” than in patients diagnosed “unsystematic schizophrenia”. Since in Fish’s study moderate to marked response to neuroleptics is more than three times as frequent in “unsystematic schizophrenias” than in “systematic schizophrenias,” the inverse relationship between therapeutic effects and TD indicates that the two classes of schizophrenia are pharmacologically distinct. Findings with CODE-DD indicate that DSM-III-R’s diagnostic concept of “major depression” is so broad that, using more stringent criteria, a large proportion of patients would not qualify for a depressive illness. In one study from over 300 patients only about one-third fulfilled CODE-DD’s criteria of “melancholia”, characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes. In another study of over 200 patients less than one-fifth fulfilled Kurt Schneider’s criteria of “vital depression”, characterized by corporization, disturbance of vital balance and feeling of loss of vitality. The discovery of the antidepressant effect of imipramine, as you know, was based on Roland Kuhn’s findings in “vital depression.” Our CODE-DD findings imply that those high prevalence rates of depression in epidemiological studies are irrelevant to neuropsychopharmacology. I had many discussions about our findings with Heinz Lehmann before he passed away.

WB: He was a giant in the field. How old was he when he died?
TB: He was eighty eight.
WB: He was your mentor?
TB: I had two mentors. My first was Dr. Sandor who introduced me into psychiatry, and my second mentor was Dr. Lehmann who introduced me into psychopharmacology. As years passed our working relationship evolved into a very close friendship.

WB: Before we run out of time let me ask you a few specific questions. Where did the financial support for your research come from?
TB: NIMH, MRC (Medical Research Council) of Canada, the State of Tennessee, and from the drug industry. The development of CODE-DD was linked to the early clinical development of reboxetine and sponsored by Farmitalia supporting clinical investigations we conducted mainly with my former Fellows. By the 1990’s our research support from industry markedly decreased because I had no interest in participating in multicenter clinical investigations organized by CROs.

WB: Could you list what you think are your major findings?
TB: Well, I discovered that trazodone and reboxetine have antidepressant properties; that Ateroid might have therapeutic effects in old age dementias, but I don’t consider those as major discoveries. My *Psychopharmacology* in the late 1960s in which I systematically presented the action of psychotropic drugs at different levels, from molecular through neurophysiological and behavioral to translate pharmacological properties into clinical effects, I think was a major contribution that had an impact on the development of the field even if that book is outdated by now and by and large forgotten. I consider my most important contribution the recognition of the pharmacological heterogeneity within psychiatric diagnoses and developing methodologies for identifying more homogeneous populations in terms of psychopathology and psychiatric nosology. I also consider our conditioning test battery for the study of psychopathology and psychotropic drug effects, a contribution.

WB: So, all your work has been clinical, not basic?
TB: The answer is yes, even if during the 1960’s I was involved in some pre-clinical research with Drs Kato and Gozsy in exploring the effects of psychotropic drugs on dextran-induced capillary permeability. I found it interesting that one could predict whether a substance is an antipsychotic or an antidepressant from its effect on dextran-induced capillary permeability. Of course if anyone would have suggested testing a hypothesis that capillary permeability changes are the cause of depression or antidepressant effects, I would have been the first to object.

WB: Do you still see patients?
TB: I was seeing patients for well over forty years and used to pride myself that I had seen several times more patients than many practicing psychiatrists together, but my current activities don’t leave me time to have even a part time practice.

WB: Tell me about the teaching experiences you’ve had.

TB: I was involved in teaching medical students, psychiatric residents, and fellows all through the years, supervising undergraduate and postgraduate students, and mentoring some of those interested in pursuing a career in our field. It was rewarding to see that *Psychopharmacology for Everyday Practice*, a book I published with Marc Hollender, was translated into Dutch and Japanese, and was used in teaching in those countries. And it has been most rewarding to see some of the Fellows trained in our WHO program, becoming professors and heads of departments in their home countries.

WB: Your teaching had an international impact. Did you have administrative responsibilities?

TB: My first major administrative responsibility was directing McGill’s Division of Psychopharmacology. The Division disintegrated shortly after I moved to Vanderbilt. And in the 1990’s I became President and Chairman of the Board of Directors of a company with my former associates that for all practical purposes died before it was born. It was probably unrealistic to form a company that was dependent on industrial support which was trying to narrow the indications of drugs. So, I would say, I failed as an administrator.

WB: You always had an open mind, contrary to some people. You published extensively throughout the years. How many papers did you publish?

TB: Over seven hundred papers, including journal articles and book chapters.

WB: What was your last publication?

TB: *The Role of Serendipity in Drug Discovery*. It reviews the serendipitous discovery of many of the drugs used in psychiatry.

WB: Where was it published?

TB: In Dialogue, a journal published by Servier, a French drug company. I was very pleased to learn from Don Kline that he found it useful in preparing for his Oakley Ray history lecture this year.

WB: Were you involved in editing journals?

TB: I was co-editor with Fritz Freyhan and Pierre Pichot of the International Journal of Pharmacopsychiatry, and also of the series, *Modern Problems of Pharmacopsychiatry*.

WB: How many books have you written?

TB: Twenty three and edited twenty seven.

WB: So fifty altogether?
TB: Many of my edited books are collections of our studies with the same drug, e.g. trimipramine, trazodone, or drugs form the same family, e.g., butyrophenones, thoxanthenenes. I used drug studies to generate information for a continuous re-evaluation of psychiatric concepts and many of my monographs are based on this continuous re-evaluation. Schizophrenia, A Psychopharmacological Approach, was followed by Recent Advances in the Biology of Schizophrenia, Depression and the Tricyclic Antidepressants was followed by the Psychopharmacology of Depression, and Psychopharmacology in the Aged was followed by Cognitive Decline in the Aged. My last monograph, Classification of Psychoses was co-authored by Ronalso Ucha Udabe, who was, as I said before, one of my former WHO Fellows. He also co-edited with me The Neurotransmitter Era in Neuropsychopharmacology, published in 2006.

WB: That’s very impressive. Can you say something about your family?

TB: I got married the day President Kennedy was assassinated. My wife is many generations Canadian. She is a graduate of the University of Western Ontario. She was a housewife until our son left for college, but after we moved to Toronto, she became an actress. Our son majored in history and political science, then, after he got his Masters in European Community Law, he became a documentary filmmaker. He lives nearby in Toronto. We are a close knit family.

WB: What are your current activities?

TB: I am editing ACNP’s ten volume oral history series on the first fifty years in the development of neuropsychopharmacology, which, in itself, is a full time job. It will complement CINP’s four volume history series, I co-edited with David Healy and Edward Shorter in which the same period was reviewed in autobiographical accounts. These two series should provide authentic, first hand information on the birth and early development of neuropsychopharmacology. I am also serving on an independent commission of inquiry, set up by the Canadian University Teachers Association to find out what led to the seizure of the research files of a group of distinguished researchers by their Institute’s ethics committee. We hope that by getting to the roots of the problem we would be able to make recommendations that could help prevent such a drastic measure being taken again. Finally I have started to develop a new methodology I refer to as “nosologic homotyping” for identifying empirically derived pharmacologically homogeneous psychiatric populations. Nosologic homotypes are identical in psychopathologic symptoms, not in the content of symptoms of course, and are assigned the same position in the “nosologic matrix,” based on three nosologic organizing principles, which are totality, temporality and polarity. They are more homogenous in mental pathology and
provide more suitable end-points for biological research than DSM-IV or ICD-10 diagnoses.

WB: I want to ask you one more question and that is about the future. What do you think is going to happen, both, in terms of your contributions or in terms of the field in the future?

TB: I believe we will identify pharmacologically more homogeneous populations in the next decades that will break the impasse of developing clinically more selective drugs, which in turn would open the path for molecular genetic research in psychiatry. I also believe that the identification of these populations will be based on research in psychopathology and psychiatric nosology and not in research on biochemistry, neurophysiology, endocrinology or molecular genetics.

WB: Is there anything else you would like to add?

TB: I would like to add that while clinical research in conditioning has been dormant, basic research in conditioning continued and by the dawn of the 21st century the structural and functional foundation of classical and operant conditioning have been discovered in the brain. So, if it would be verified that the abnormal connections between and across mental structures, the structural basis of psychopathology, are CR connections, as some structural psychopathologists suggest, I could imagine, by letting my fantasy fly, that CR variables would provide a "code," something like the genetic code, that would define psychiatric disorders. The idea of course is not new. Its roots are in the research of Griesinger and Pavlov.

WB: Did I miss anything?

TB: I think we covered everything important and even some of my fantasies.

WB: I see you as being there from the very beginning, continuously active in research, writing a huge number of papers and books and communicating across the different areas of our field. We talked about Heinz Lehmann, one of your mentors, being a giant. I think you also are a giant in this field. I really enjoyed talking with you and having a candid interview.

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

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

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

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

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

FB: A pharmaceutical company became interested and bought it.

TB: So, it was used?

FB: It's still being used.

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

FB: I was about 22 years old.

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

FB: I accepted a position at the Czechoslovakian National Institute for Public Health. It was the Czechoslovakian NIH, and I did primarily bacteriological research, related to typhoid and paratyphoid. It was just discovered that the various parathypoids can be typed and identified. This was of great public health interest, because of the many kinds of dysentery and food poisoning. I was fortunate I could do research in bacteriology as a medical student and continue research in that field after graduation.

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

FB: All my findings were published.
TB: When did you have your first publication?
FB: In 1935.
TB: So you had your first publication when you were 22 years old?
FB: And I had a publication almost every year after that.
TB: So you had several publications by the time you left Czechoslovakia. How old were you when you left?
FB: I left Czechoslovakia in 1939 when I was 26 years old.
TB: Could you tell us about the circumstances when you left and something about your family?
FB: Hitler occupied Czechoslovakia in 1939. My mother was Jewish, and people who were of Jewish origin were not welcome any longer. I expected that this would happen, so I was ready to leave. I had an uncle in the United States, who I persuaded to send affidavits for myself, my girlfriend, my parents, my brother and my sister. With his guarantee we had our passports and visas that permitted us to enter the United States. Hitler came on the 14th of March, I believe. I married my girlfriend on the 15th, and on the 16th got on the train with her and my brother and left for America. My sister and parents couldn’t be persuaded to leave. We were not allowed to take any money with us, only what we could carry in our bags. But I was happy to go. We left by train to Holland, where we intended to board our ship to America, but when we arrived we were told that we could not board the ship because the United States declared all visas issued to Czechoslovakian citizens invalid. We were also told that we could stay in Holland for one week and, if we didn’t find a place to go we would be deported back to Czechoslovakia. We were fortunate in obtaining entry to the United Kingdom through the generosity of an English lady, whom I never met. She was a Quaker. As soon as we arrived in England I wanted to thank her, but she discouraged me. It is thanks to her, that I’m here today.

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

TB: That was in 1939?

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

TB: What position did you apply for?

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

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

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

TB: We don’t see diphtheria any longer.

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

TB: What year was that?
FB: In 1943.

TB: I suppose you had to work day and night in the hospital.
FB: Oh, yes. It was a strenuous job but it was important to do it and I’m glad I had that experience.

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

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

TB: Did you publish your method?
FB: Yes, I published it in Nature.

TB: Was this your first publication in English?
FB: Yes. At a time people didn’t want to publish any article that might help the enemy. But I resisted keeping it a secret.

TB: You felt that the benefits of your discovery should belong to everybody?
FB: Sure. So many lives depended on surviving pneumococcus and streptococcus infections. There was nothing else to treat them. I published it in Nature, I believe, in about 1944.
TB: What happened afterwards?

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

TB: Where were they located?

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

TB: What was your position at BDH?

FB: I was working in the research department. BDH was one of the most important firms at that time in England, but the research department was not large. My task was to develop a way to protect penicillin in solution from Gram-negative penicillinase producing bacteria. It was to find a non-toxic agent which killed Gram-negative bacteria. One such agent was phenyl ether of glycol, called phenoxitol.

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

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

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

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

TB: Why was that?

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

TB: What did you find?

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

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

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

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

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

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

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

TB: What was the response to your paper?

FB: There were a lot of reprint requests. So, I corresponded with some people in the United States and they encouraged me to go to America. I needed some encouragement, because at that time it was not permitted to prearrange a job before arriving to the United States. You had to swear that you made no prearrangement. So, I didn’t make any but I did prepare a list of people who requested reprints. I arrived in America in October 1947 and called or wrote to the people on my list and told them that I was in America and looking for a job.
TB: Am I correct that you arrived with your wife and your older son, Franklin.
FB: Franklin was born in 1949. It was just my wife and I.
TB: Did your brother stay in England?
FB: My brother returned to Czechoslovakia in 1945, after the liberation. He went back, claimed his inheritance, and started a new life with the intention to stay in Czechoslovakia. It didn’t do him much good, because after the communists took over the country everything was taken away. Then he came to America.
TB: Did you have any problem with the immigration authorities when you arrived?
FB: I had no problem. My uncle sent me the necessary papers. But I had to swear that I didn’t have a job. There was another limitation at that time; you couldn’t bring more than three hundred dollars with you. So, I didn’t have much time to find a job. But I got in touch with the people on my list, and one of them, Dr. Bass who is here in Nashville, invited me and offered me a job. He was most kind to me. At that time he was professor of pharmacology at the University of Syracuse in New York.
TB: So it was Allan Bass first who offered you a job.
FB: Several people who read my paper knew I needed a job. He was one. There were others, for example, Dr. Schlesinger at Columbia, Dr. Schwartz at Rochester, and Dr. Blancard at NIH.
TB: Your arrival in America was different from your arrival to England.
FB: Absolutely. I was a little short of cash, but I had a job in less than a month.
TB: It was good that people responded so promptly.
FB: I was much better known by the time I arrived here. People here knew about my work with mephenesin and were very friendly and generous. It was very different from my arrival in England.
TB: What was your first job in the United States and how did you select it?
FB: I knew nothing about the American system, but I had a very good friend here, George Blancard. He is an American by birth but we went to medical school together in Prague. We became friends at medical school and after he returned to America, he worked at the NIH. It was George Blancard, who advised me to accept a university position in Rochester, New York. I did, and enjoyed it.
TB: How long did you stay in Rochester?
TB: Till the end of 1947. I was Assistant Professor of Pediatrics, but my main interest was research. I wanted to continue my research with mephenesin because I was fascinated by its unusual effect on the central nervous system. I needed some very expensive equipment, electroencephalographs and oscilloscopes. I was advised to apply for it. So I did, and
was very fortunate; I obtained all the things I thought I needed. They were obtained through collaboration with the department of chemistry where people made compounds for me. My aim was to produce something that would do the same that mephenesin does in smaller doses and for a longer period of time. So, the first thing that I did in Rochester was to find out why mephenesin is so short acting. It was one of the shortest acting drugs known. When you swallow a tablet, you can show the presence of it in the urine in less than half an hour. So, a chemist in the department produced various compounds and I let people help me determine which part of the molecule of mephenesin makes the drug short acting, so it could be blocked. My objective was to modify the molecule so that the action was more prolonged. After it had been identified that it was the part of the molecule attacked by OH groups, the plan was to prepare compounds where the OH group would be blocked. These compounds were prepared and evaluated but, as a whole, they didn’t act much longer than mephenesin, or if they did, they were pharmacologically not more powerful. Meanwhile, I thought I’d get into studying mephenesin’s action in human beings, so I was looking for somebody to prepare a supply of mephenesin tablets that I could give to patients. Ultimately, it was done by Squibb. I had a clinic of people with neurological and psychiatric disorders on whom I tried tablets. I tried it first on cerebral palsy patients and found that, in spite of the short duration of action, it did relieve to some extent, not only their muscle spasms but also the involuntary movements. I tried it in Parkinson’s disease and found it also affected, for a short time, their symptoms.

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

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

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

FB: Yes, in Britain.

TB: But not here?

FB: Not here and even in Britain only for intravenous use and that was just impractical. There’s a constant risk of hemolysis given IV mephenesin, but it seems to be safe orally. I had about 200 patients with cerebral palsy, Parkinson’s disease and all kinds of involuntary movements and I tried it in many of them with fair results. I published it in the Journal of the American Medical Association. Very much to my surprise, the paper was accepted and created great publicity. It was written about in newspapers in 1948 and Squibb managed to get mephenesin approved by the Food and Drug Administration. It came out on the market and became their best selling drug.
TB: It was a gift to Squibb; it seems you did all the work. All that Squibb had done was get it approved and marketed. At this point you were still employed by the University of Rochester?

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

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

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

TB: You’d already handed them a gift!

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

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

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

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

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

TB: How did you do that?

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

TB: By screening?

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

TB: Was this meprobamate?

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

TB: What happened with the other compounds?

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

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

FB: The first thing with meprobamate was to establish its lack of toxicity. We had an outside agency making meprobamate for us and it was not easy to find one. Finally I persuaded Bob Milano, the president of a small chemical plant in New Jersey to set up facilities for manufacturing the drug. It was the company that manufactured the first tablets of mephenesin for Squibb. I told them I was the man who discovered mephenesin and I had something better, so they did it at an affordable cost. We needed a lot because I would not let anybody give it to a human until we had finished one year of toxicity in several species, although that was not required at the time by the Food and Drug Administration. I just did it because I wanted to sleep at nights.

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

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

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

TB: What kind of patients did they study?

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

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

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

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

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

TB: How did you get to the name?

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

TB: What year was that?
FB: That was in 1955.

TB: Could you tell us something about Dr. Borrus’ study? How many patients were involved?
FB: Approximately 150, maybe 200.

TB: What kinds of patients were involved?
FB: Those were all psychoneurotic patients.

TB: If I remember Leo Hollister was working with meprobamate in schizophrenic patients. What about Karl Rickels?
FB: He had a mixture of patients.

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

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

TB: We are now in late 1955 and 1956. Meprobamate is available for clinical use as Equanil and Miltown in the United States. What about the rest of the world?
FB: Equanil was sold by Wyeth all over the world. Wallace Laboratories became big and Carter Products changed its name to Carter-Wallace. Then they wanted to be recognized on the Stock Exchange and I helped them do that.

TB: When did this happen?
FB: In 1956. That was a very interesting experience.

TB: Didn’t you become president of Carter Wallace? When was that?
FB: In 1955. When I took over Wallace Laboratories, the annual sales were $80,000. In 1956 the annual sales were about $200,000,000.

TB: You created not only a drug but also a company!
FB: Yes, a company that was listed on the New York Stock Exchange.

TB: Did the company grow as years passed?
FB: I gradually built it up to about a hundred people. I had plans for other products; I never forgot my love for microbiology. I had about thirty or forty people just in that field. The basic problems that interested me there was that not everybody who gets infected gets sick. Not everybody who comes in contact with typhoid or tuberculosis develops a disease. Why is that?
Frank M. Berger

Later on that was to become your primary interest. But during the late 1950s and even in the 1960s you did extensive research with meprobamate.

Yes.

Could you say something about that research?

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

So, Ralph Gerard was involved.

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

There was an important meeting on meprobamate in New York?

That was at the New York Academy of Sciences in 1956. By the middle of that year over a hundred papers had been published on the effects of meprobamate. It was a world in which tranquilizers like meprobamate were used, abused and misused. I felt it was high time to arrange a conference to review the state of art about the use of tranquilizers and find out what writers and philosophers also think of the new era in psychotropic medications. I thought it would be a good idea to invite the Huxley brothers; Aldous Huxley, a great writer who was always very much interested in substances affecting the mind, and Julian Huxley, a biologist and philosopher. They both agreed to speak at that conference. We also had leaders in various professions; Ralph Gerard, one of the leading neurophysiologists, Jim Miller a Professor of Psychology and Psychiatry, Harry Beckman, the President of the American Pharmacological Society, and many others. We had this two-day conference and published the highlights. The meeting also had another purpose. At that time, many doctors and most laymen didn’t differentiate between antianxiety and antipsychotic drugs and, I tried to make it a point at the meeting that there are differences between these new drugs. On the one hand you have substances like chlorpromazine and reserpine with an effect on the autonomic nervous system which affect severe mental disturbances, such as schizophrenia, and control hallucinations and delusions. And on the other hand you have substances such as meprobamate or mephenesin that do not affect the autonomic nervous system, but are effective in relieving tension and anxiety. That was an important point to make. And another important point was that anxiety is not a normal condition.

Could you elaborate on your thoughts about anxiety?

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

TB: It is an important distinction.

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

TB: Did you collaborate with Cattell?

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

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

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

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

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

TB: Did the people who owned Carter Wallace recognize you made their company the most prosperous in the country? Did they compensate as you deserved?
FB: At the time I was hired in 1949, long before meprobamate appeared on the market, we had signed an agreement that I was entitled to a royalty of one percent on sales up to seven and a half million. There were no sales of any kind in that range at the time. I made forty thousand dollars a year and I thought that was a lot of money. It was. But when meprobamate came it sold more than two hundred million dollars a year, the profit, after costs and advertising, was more than thirty percent; thirty percent clear profit, sixty million dollars. They had given me seventy-five thousand dollars on a sixty million profit. I thought I should do better than that. After lengthy discussions, I did a bit better. I got four percent, but I never managed to eliminate the seven and a half million upper limit.

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

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

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

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

TB: When was Soma introduced?

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

TB: The primary indication for Soma is pain.

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

TB: Any important other drug after Soma?

FB: One was tybamate, another antianxiety drug.

TB: When was tybamate introduced?

FB: In the early 1960s.

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

FB: Yes.

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

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

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

FB: Not really. They were free to use the techniques I developed. I published them so that other people could use them. I feel that in medical science everything should be published. It’s all right to patent a compound because the patent lasts only for several years. It just gives an inventor a personal reward. But the technique used to make the invention should not be secret. It should be public so that other people could use it in order to develop even better drugs.

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

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

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

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

TB: What happened to those compounds?
FB: They were not patented, so nobody is interested in them any more.

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

TB: Compared to the market of meprobamate that was a small market.
FB: The drug I discovered for epilepsy was first patented in 1950. I did some studies in humans at Brown University. It was good but they just did not want it. But after I left the company they revived it.

TB: When did they revive it?
FB: In 1980 or 1985. They combined it with another substance and got a new patent.

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

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

TB: When did the problems start?
FB: I think the problems started in the late 1960s.

TB: What happened?
FB: Mr. Hoyt, the owner of the company was getting old and he told me, “You are a scientist. You still don’t know how to read a balance sheet properly, and I want my children to have a safe and solid business. I want this company to run as a business and not like a charitable organization. I will ask a leading firm that advises management how to improve business and to investigate this whole set up”. He hired a firm from Chicago that was well known in this type of study and they suggested I should be responsible only for the scientific part of the company. Everything else was taken away from me.
TB: This happened in the late 1960s?
FB: In the late 1960’s and there was nothing I could do about it, because all the voting stocks were controlled by Mr. Hoyt.

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

TB: You wanted to remain your own boss. What did you do after you left?
FB: I left in 1973 without any severance pay and I retired. I was about 59 years old but I did not start playing golf. I became a consultant to many firms in Europe and in this country, and participated in developing various immunological products.

TB: So you returned to your first interest, microbiology and immunology.
FB: Yes, but I never got enough financing to develop any of the products. By the time I got it going I was 65, and by the time I had it all ironed out I was over 80. It’s very difficult to get financial support at that age.

TB: Were any of your products for immunology developed?
FB: Carter Wallace developed protodyne later on.

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

TB: So it went down even below the level it was before meprobamate.
FB: But they still prosper because they acquired Trojan condoms, shortly before the outbreak of HIV. This is now their main business.

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

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

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

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

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

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

TB: Anything else you would like to tell us?

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

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

FB: Thank you very much.
TB: I am interviewing one of the pioneers of psychopharmacology, Dr. Jonathan Cole for the Archives of the College. My name is Thomas Ban. Would you tell us where you were born and something about your education and early interests?

JC: I was born in Boston and raised in Cambridge. My father was a professor of Economic History at Harvard and was eminent enough to be head of the American Economic History Association and have a room named after him at Harvard’s Baker Library. He was a somewhat austere man, who looked like he’d been to Oxford or Cambridge, but had in fact been raised in Haverhill, Massachusetts. My mother was of Pennsylvanian Dutch extraction, and on her side there was a fair amount of money, so we lived comfortably. I went to private schools and opted for science vs. history, at some point. I was in my last year of high school during 1942, when Pearl Harbor occurred, and after graduating in the spring I went directly to Harvard, did pre-med, and got into medical school four terms later. I was sixteen when I got out of high school, because my mother made me skip the first grade. Without that, I would have died in the Battle of the Bulge. Instead, I was in medical school at Cornell by that time.

TB: You knew by the time you graduated from high school that you wanted to go to med school?

JC: In the tenth grade, you had to choose whether you took history or science and I chose science. I was not well coordinated, as a kid, so I was not sure I could be a doctor. My first year at Harvard I got an A in dissecting a frog brain and decided if I could do that, I could probably make it through medical school, despite critical noises from our housekeeper, who was sure I was a twatz and would never go anywhere. Actually, my father thought that too. My father was a good athlete and I was lousy.

TB: So, you went to Cornell?

JC: Probably because I needed three people to represent me to go to Harvard and I didn’t know three. At Cornell, they only required two. I applied and was accepted.

TB: Is there anyone who influenced your career choice?

JC: My mother made me read a fair amount about medical discoveries and in my teens, I read Arrowsmith, by Sinclair Lewis, and thought doing research and discovering cures would be wonderful.

TB: Books can have a great impact on people’s lives.
JC: Yes. As a teenager my best friend’s older brother, after Harvard, took a job with Gillette and the idea of finishing college and going to work for a big corporation struck me as creepy. Medical school, on the other hand, sounded orderly, predictable and secure. It was probably to avoid getting into unknown waters that I figured it would be best to get into medical school.

TB: How did you become interested in psychiatry?

JC: During medical school I became interested in pharmacology. The department at Cornell was unique because Harry Gold was doing studies with placebo on anginal pain, insomnia, and the symptoms of arthritis, demonstrating that placebo had substantial effects on those symptoms. Then, I read Freud while we were doing bad things to dogs in the physiology lab, and I wondered whether their response to what we were doing was due to their early life experiences. But, probably the most important factor that led to my decision was that my mother had bipolar illness that came on after a hysterectomy and spent the better part of her life in psychiatric institutions. So, I’d seen a lot of psychiatric hospitals. She would be wildly manic for a while, then very depressed. I thought during the first two years of medical school that I couldn’t become a psychiatrist, because I hadn’t majored in psychology, but by the third year it became clear this was not true. During that same year, I had a very good teacher in psychopathology who gave some lectures at Manhattan State Hospital, where I got to see a fair amount of severe psychopathology. I also did one summer during medical school at MacLean’s Hospital in Boston and greatly enjoyed having lunch with the psychiatrists. They were more fun to talk to than most people that I knew, so I decided that I wanted to end up in psychiatry.

TB: Did you do any research as a medical student?

JC: I mistreated some rabbits, as an experiment in pathology. I was interested in why some people have resistance to disease whereas others don’t. We chopped the skin of rabbits and injected the protein to see whether you could create antibodies against it. I wouldn’t say our research was a great success.

TB: I see. When did you graduate from med.school?


TB: You went straight into psychiatry?

JC: No, I did a year of internal medicine at Peter Bent Brigham Hospital in Boston.

TB: And after that into psychiatry? Where did you do your residency?

JC: At the Payne Whitney Clinic, part of Cornell in New York.
TB: I suppose psychiatry was psychodynamically oriented at Payne Whitney in those years?

JC: Yes and no. Our chairman was trained by Adolf Meyer. His attitude was you could only be psychoanalyzed during residency if you were screwed up enough to need treatment. I think he also thought that being psychoanalyzed would take you out of the hospital for about two hours a day for at least four days a week which was bad for getting work out of the residents. He met with pairs of residents for three hours a day, one day a week, and went to the wards to see each of your patients. Supervision was extraordinary by present day standards. You hardly saw outpatients and almost never saw a child, but saw a bunch of inpatients. You learned how to write five-page, single spaced, case presentations which you had to give after the patient had been there about six weeks. You also learned how to comment on other people’s cases.

TB: Did you do any research during your residency?

JC: You were supposed to present a paper. I read everything I could find on psychiatric reactions to ACTH and cortisol and presented a review, but I never could figure out anything useful to do in the way of a study.

TB: Who selected your topic?

JC: I’d seen some patients getting very happy on steroids while I was an intern at Brigham with George Thom, who was an expert on the adrenal gland. We had a lot of Addisonian patients who were on cortisone that had just become available. I was also marginally involved with an ergot alkaloid, tested in hypertension, when I was a resident at Paine Whitney. It didn’t work very well.

TB: Was it ergoloid mesylate (Hydergine)?

JC: No. I think it was a precursor or analog of it, but I wasn’t really the one who was doing the study, I was more of an observer. My best friend in residency was interested in child psychiatry and when triiodothyronine (Cytomel) came along, he gave some to a five year old autistic child, who started talking for the first time.

TB: As a resident what kinds of treatments did you use?

JC: The only treatment we had was ECT. I was impressed with it. I also did some sub-coma insulin, but I think in the wrong patients. We treated very disturbed patients and it didn’t seem to me it did much.

TB: How was ECT given in those days?

JC: We took the patients to the ECT room, laid them on a firm mattress, put a big rubber band around their head with electrodes and zapped them, while everybody leaned on them so they wouldn’t jerk too much.

TB: Any other treatment?
JC: We used Amytal (amobarbital) IV for interviews and orally as a sleeping pill. We also had barbital (Veronal) for daytime sedation and that was about it. I remember a depressed man who told me, “Doc, when I get depressed I need thirty milligrams of dextroamphetamine (Dexedrine) at night because I can’t sleep and it makes me sleep like a log and I will get better”. So, I gave him thirty milligrams of Dexedrine and he did sleep like a log, but he didn’t get better.

TB: Anything else you would like to say about your residency?

JC: I remember that there was one social worker for a hundred and seven patients, so the residents had to take their patient’s family histories. We were also trained to do the Wechsler intelligence testing. I’d also had a course on it in medical school so I got to be pretty good doing it.

TB: So you became expert in administering the Wechsler?

JC: Yes. By the way, Jolly West was a year behind me in residency and supervised me in hypnotherapy with a patient, which was fun. He had learned the technique in high school.

TB: You did hypnotherapy as well?

JC: I did that in only one patient, a pediatrician, who was a cross dresser. He had been unable to penetrate his wife after a year of marriage, but with hypnotherapy she became pregnant in six months. Everybody was quite satisfied with the result.

TB: What did you do after residency?

JC: I went into the army. After basic training in Texas, I spent about eleven months in North Carolina, and then I was shipped out to Japan for a year. I spent most of the time in Fukuoka in a small army hospital where I was the only psychiatrist. I met and married my first wife, a social worker, while in the army. During the time in North Carolina I was working on an insulin coma ward.

TB: You did insulin coma treatment in an army hospital?

JC: I also gave lots of ECT.

TB: As a resident, if I remember well, you said that you used only modified insulin. Did that create any problem?

JC: I had a very good manual on insulin coma therapy from the Institute of Pennsylvania Hospital, which gave you a step by step description of how to do it, what to expect and when to stop. And I didn’t do prolonged comas so the whole thing turned out very nicely.

TB: You think insulin coma worked?

JC: I remember only two cases where it did not work. One of them just got fatter and fatter. The other was an angry African-American, whom we could not get to go into a coma. He would get a little fuzzy and then start to scream, become excited and agitated, but never went into coma. We
tried for about three or four weeks, then gave up. We did everything the manual suggested and a couple of other things. I remember those two failures and ever since I’ve been intrigued with insulin coma therapy. If somebody would give me a grant, I would try it again.

TB: You would?
JC: It’s no better than antipsychotic drugs but whether they are the same patients, who respond, haven’t been tested.

TB: Did you have any contact with Joe Wortis in those days?
JC: No. I met him later, but I never talked about insulin coma to him.

TB: He was the one who introduced insulin coma here after meeting Sakel in Vienna.
JC: Yes. He went to Vienna to be psychoanalyzed by Freud and came back with insulin coma.

TB: So your experience with insulin coma was positive but with modified insulin it was negative?
JC: Yes, but we used modified insulin mainly in disturbed schizophrenic patients on a female ward. I think it was inappropriate, in retrospect.

TB: What about drug therapy.
JC: We used barbiturates and I presume chloral-hydrate was there.

TB: What did you do in the army hospital in Japan?
JC: I did outpatient consultations. It was very good for me, because I saw a lot of people who were illiterate, people with three or four grades of education that I hadn’t seen at Payne Whitney. At Payne Whitney, if you couldn’t play bridge or you didn’t have at least a year of junior college, you were ostracized. So I learned how to get along with people from the hills of Arkansas. There was some drug abuse in Japan by soldiers and I presume by the Japanese; I think they were using speed type drugs but we mistakenly thought they were opiates. It didn’t matter because you got discharged from the army, no matter what you used. But I think I was diagnosing heroin addiction in people who were using methamphetamine.

TB: From Japan, you returned to civilian life to do what?
JC: I figured that I’d been at Payne Whitney so I’d go somewhere else. I arrived home to find a letter asking if I was interested in a job at the National Academy of Sciences, National Research Council in Washington, as a professional assistant and executive secretary to a number of research committees. This sounded interesting to me and I sent back a positive response. They interviewed me and hired me. So, I got onto the national scene. There were two committees I attended, advising the army on psychiatry and on stress. The stress one was run by George Thorn, who was chief of internal medicine at Brigham Hospital. There was also a committee on research about sex funded by the Rockefeller Foundation, a
committee on alcoholism funded by the Licensed Beverage Industry and, the most important one, a committee on problems of drug dependence.

TB: When was this?
JC: It was from 1953 to 1956.

TB: Tell us what you actually did during the years you spent with those committees at the Academy?

JC: My job was to take minutes of meetings and to prepare, as secretary, the grant applications we received for the members of the committee to decide about them. It was very much like preparing the material for an NIMH study section.

TB: Could you tell us something about the Academy?

JC: The National Academy of Sciences was created by Lincoln during the Civil War, with the idea that it would provide independent advice to the government. At the time I was with the Academy chlorpromazine and reserpine arrived on the scene and the Committee on Psychiatry suggested I go to NIMH to find out what they were doing about these drugs. So I met with Seymour Kety, Ed Evarts, and a couple of other people and learned they were thinking of giving a grant to Ralph Gerard from the University of California to hold a conference on How Do You Evaluate Drug Treatments in Psychiatry. My appearance on the scene apparently convinced them to use the National Academy of Sciences as the agency to do the legwork in setting up the conference with Ralph Gerard, as principal investigator.

TB: Could you tell us something about Ralph Gerard?

JC: Ralph Gerard was an interesting man. He was a neurophysiologist, who had done major work in analyzing the national need for physiology. By the time the conference took place he moved from California to Michigan and was trying to set up an empire there. He was more interested in getting a big grant for his studies than in the conference. He was strictly an advisor and wasn’t actively involved in anything. He had a very quick mind but his wife had developed cancer at the time.

TB: Where did the conference take place and how exactly did it turn out? The topic was exciting.

JC: The conference took place at the Statler Hilton Hotel in Washington in the fall of 1956. It worked out reasonably well. We had about five concurrent sessions, probably unwisely, and we tried to record all the discussion. Then I had to edit it all. I ended up as senior editor, after having a power struggle with Ralph Gerard. I felt I did 80 percent of the work.

TB: It was, for you, a learning experience.

JC: Among other things I learned that if you have federal grant money, it won’t pay for coffee or doughnuts but you can get the hotel to charge you more
for the use of their rooms and then they can include coffee and doughnuts, for free. I enjoyed finagling the system to a mild degree; it intrigued me!

TB: I see.

JC: It was while I was preparing for the conference meeting that Nate Kline and Mike Gorman testified before Congress that two million dollars should be appropriated to the NIMH to do a multi-hospital efficacy study of chlorpromazine and reserpine in schizophrenia. Their testimony included probably the first research design of a study ever presented in congressional testimony.

TB: Could you tell us something about Nate Kline and Mike Gorman? Who were they?

JC: Nathan Kline was head of psychiatric research at Rockland State Hospital in New York State and Mike Gorman was a reporter, who had written a book exposing public mental hospitals. I think they were representing Mary Lasker who had a very rich husband, and used her husband's money very effectively. She would help support people like Nate and Mike to lobby the congress and, then, she would give some money to people like Lester Hill, who was already in the House, to serve as catalyst to get the kinds of appropriations she felt were needed to treat various diseases. She was very wise about how to use soft money to achieve a great deal of leverage in getting money appropriated. And, it worked very nicely. Anyway, two million dollars got appropriated for the research but they needed somebody to run the program. As far as I could tell I was, apparently, the only visible psychiatrist who knew how to review grants. And I was willing to move. All of a sudden, from first lieutenant in the army, I was offered a colonel's commission in the public health service. I accepted the job and moved to NIMH.

TB: When was that?

JC: After the conference.

TB: Could you tell us who participated in the conference?

JC: Representatives from the drug industry and representatives from academia.

TB: What was the title of the proceedings?

JC: *Psychopharmacology Problems in Evaluation*. It was published by the National Academy of Sciences and the National Research Council. I think I still have three copies at home. If the ACNP doesn't have a copy for their archives, I ought to send them one before they disappear. The book was not a vast commercial success. I think a thousand copies were printed and about a hundred were left, which the academy gave to me to get rid of. I've given them to various people since.
I have actually a copy of that conference in 1956. We had chlorpromazine and reserpine by that time, but we didn’t have imipramine and iproniazid as yet.

Imipramine was certainly not on the market; it became available two years later. Meprobamate (Miltown, Equanil) was already on the market and was selling like hot cakes. Frank Berger, having discovered it, received a lot of publicity at the time. FDA did not require efficacy for a drug to be marketed in those years, only safety. In 1956 there was a conference on meprobamate at the Waldorf Astoria in New York.

I think the Huxley brothers, Aldous and Julian were there.

I don’t know. I wrote my first formal paper for that meeting and I got paid two thousand dollars.

What was it on?

It was a historical review of treatments.

You said, it was your first paper?

Yes. The only thing I had ever done before at the Academy was a bibliography on fatigue.

Could you tell us more about that review?

I reviewed some of the recent papers on chlorpromazine as well as old treatments but not only pharmacological treatments. One of the most outrageous treatments was based on the assumption that psychiatric illness was due to infection and the treatment was getting rid of anything that might harbor an infection. They pulled all the teeth, cleaned out the sinuses and removed the colon.

The colon? Where was that done?

At Trenton State Hospital. They had a very high discharge rate; people didn’t want their colons removed. I covered the treatment of neurosyphilis with penicillin, comparing it with malaria treatment. I also got into literature on the treatment of parasites and, reviewed insulin and electric shock.

What about treatment with vitamins?

I didn’t come across much because that didn’t get written about. I did touch on it later through Abe Hoffer.

I was thinking of nicotinic acid in pellagra and thiamin in the amnestic syndrome.

They used to say “if you find a nice cure for something like pellagra with Vitamin B₃ and penicillin for cerebral syphilis, those patients get taken over by general medicine and you never see them again”.

We are in the late 1950s when you got to NIMH. You certainly were the right person for the job.

I was handy and they couldn’t think of anybody better who would come on such short notice. I also came with a good deal of humility; wasn’t sure
what I was going to do. I was helped in the first year by Sherman Ross, who was professor of psychology at the University of Maryland. He had the longest and most heterogeneous publication list that anybody had ever known. He had one paper called, “Gorilla-Gorilla-Gorilla” and at the other end he had papers on industrial psychology, on psychometrics and even a paper on coca-cola. He never got a chairmanship because he wouldn’t focus on anything. But, he knew a great deal and was on sab- batical. So, I had him as a consultant to help me set up a psychopharmacology program and he proved very useful, both in teaching me research and recruiting staff to help run things.

TB: Could you name them?
JC: Sy Fisher, Marty Katz and Dean Clyde.

TB: When did they join you?
JC: Some of them came in late 1956

TB: And what was your mandate, evaluation of new drugs?
JC: I didn’t feel capable of that. The first year was spent recording existing grants to make them look like psychopharmacology. We ended up with a list of grants like Carl Pfeiffer’s, a big sloppy grant, mainly about epi- lepsy, but there was a section in it about whether it would be interesting to give schizophrenics a sedative and see whether it worked. We had a grant that dealt with carbon dioxide which was a biological treatment by a basic scientist at Penn, who was studying the effect of carbon dioxide on the brain, Scrounging around, recoding things that might just barely have a possible role in psychopharmacology, we came up with about eight hundred thousand dollars worth of stock to report to Congress by December. I turned out to be good in writing reports to Congress, so throughout my time at NIMH, I did what one might call the science writing, I wrote the reports for congressional inquiries and that sort of thing.

TB: You wrote the reports?
JC: I wrote the reports. And, then, in July of 1957, Jerry Klerman came for two years on a military draft exemption. Those were the days when you had to do two years in the military. If I would have been wise enough myself, I could have spent my two years in NIMH, rather than with the army in Japan; although, it was probably good for my education to be in the army. So Jerry came and I hired him; he was obviously very good. Then I hired Sol Goldberg, a psychologist, and the three of us planned the nine hos- pital collaborative study, which did what Nate Kline had in mind, compar- ing promazine, thioridazine, fluphenazine and placebo in newly admitted, first or second admission, patients with schizophrenia. It is interesting to compare what we did then and how we do things these days. We had enough money to do the study, so we went to the APA meeting that year
and solicited people to write an application if they were interested and capable of doing a study which would require admitting one hundred and twenty patients with schizophrenia in two years. There was only one application that was not approved.

TB: Do you remember the participating hospitals?
JC: DC General, Springfield State Hospital, City Psychiatric Hospital in St. Louis, Rochester State Hospital, Manhattan State Hospital, and the Payne Whitney Clinic. We also had a hospital in Danville, Kentucky, The Institute of Living, and Stonybrook and one of the private hospitals in upstate New York.

TB: So, the study was designed by you and Gerry Klerman?
JC: Together with Sol Goldberg. And we also appointed a review and an advisory committee.

TB: The primary criterion in the selection of hospitals was to have enough schizophrenic patients?
JC: Yes but they had to show they could organize and run it well, It was interesting that drop-out rates were zero in hospitals where the superintendent was the principal investigator. One of these hospitals was in Rochester, another in New York, a third in Danville and Springfield State Hospital. In these hospitals there were no dropouts, for any reason, during the six weeks of the study.

TB: What was the overall dropout rate?
JC: It was about twenty-five percent. The highest dropout, fifty percent, was at the DC General Hospital in Washington, followed by the City Psychiatric Hospital in St, Louis, Missouri.

TB: Was the diagnosis based on DSM-II criteria or simply a clinical diagnosis?
JC: We had no diagnostic instrument, but we could go and look at the Lohr scale data for these patients. John Davis still has the data on tape, because he reanalyzed it about twenty-five years later.

TB: Wasn’t the Lorr scale the main assessment instrument in the study?
JC: The Lorr and the Burdock scales. We probably also had a global improvement scale, but I can’t remember. We never knew what to do about side effects. We recorded them, I can’t remember how.

TB: Do you think that in some of the patients the diagnosis might have been wrong?
JC: I presume, in retrospect, that maybe a third of patients were schizoaffec-tive psychoses, or at least ten percent were psychotic patients with mania and probably a few amphetamine psychoses were also in there.

TB: How did you decide about the sample size?
JC: We had statisticians at NIMH and asked them how big our sample should be. The answer we received was, and I quote, “As many as you can get”. We did not do any estimation of the effect size or anything like that.

TB: I assume by that time you had quite a bit of experience yourself, with chlorpromazine and with some of the other phenothiazines.

JC: No, I didn’t.

TB: You did not.

JC: I’d had one anxious lady I saw before I went to NIMH, and she was complaining of stiffness in her knees. She thought she was getting arthritis. It turned out she was on reserpine for her high blood pressure and had early Parkinson’s from it. That was about as close as I got. Of course, I had been to a lot of meetings and talked to a lot people.

TB: You didn’t have a private practice in the years when chlorpromazine and reserpine were introduced?

JC: No. I went to meetings, talked to people and guys on the advisory committee with experience. I think that worked reasonably well.

TB: Who was the statistician involved in the analysis of your collaborative data?

JC: I think it was Dean Clyde. He had experience with computers back in the days when we were key-punching the data. The kind of thing I would do is to make sure the contract got to people; the study was set up right, and looked okay.

TB: Could you say something about the results?

JC: The three drugs were usually better than placebo. We had about eighty-five dependent measures and on none were any of the drugs significantly different from one another. It should have been a couple, by chance alone. We played around with predictors of improvement and found that disorganized schizophrenics did better on chlorpromazine and paranoid patients on fluphenazine, but in a second study it didn’t replicate. By and large, the history of trying to replicate predictors in drug responses has not been too successful.

TB: Remind me, what was the duration of the study?

JC: Six weeks if my memory is correct. It wasn’t longer than that. We then did a twenty-six week study, in which we used the three drugs but no placebo with a couple of other hospitals included, and what we found was that there was not much further improvement after the thirteenth week. And, our impression was that negative symptoms did about as well as positive symptoms.

TB: If my recollection is correct, in one of the first reports it was suggested that negative symptoms respond to drugs only, whereas positive symptoms are placebo prone.
JC: The total improvement was better in the positive symptoms, if you included everything, but the drug placebo difference was greater in the negative symptoms. We went on and did a high dose vs. low dose study. We tried to figure out what a high dose of chlorpromazine should be and we never got a clear answer. We ended up with two 2000 mg as a high dose, but investigators would say things like, “I have one patient up around 5000 mg a day and he begins to look better.” But two 2000 mg seemed like a reasonable upper level to me.

TB: Could you tell us about some of the other programs of the Psychopharmacology Service Center?

JC: We were given enough money to do a lot of things. One of the things we did that worked very well was the Information Center in Madison, Wisconsin.

TB: I see. Could you give some background to the Early Clinical Drug Evaluation Units, the ECDEU program?

JC: In traveling around, I encountered a lot of places, mainly state hospitals, but also at some universities where people were getting funded by industry for a few months or a year or two and then the funds would drop off, making it hard to retain good staff or keep an organized program. It seemed it would be reasonable to give some centers sufficient support for a structure that would keep them going for several years and give the investigators a chance to do some studies of their own design. I remember Heinz Lehmann telling me he wanted a cost accounting study to be done for a Smith, Kline & French study because he thought that if SKF paid for the whole thing, it would have been three times what they actually paid. They were getting a lot of support from the institutions where the investigators were working. So, I suggested to the head of NIMH, who in turn proposed it to Dr. Shannon, the head of NIH, to set up and fund the ECDEU program.

TB: We are talking about 1960, approximately, right?

JC: I think that’s about right. It came after we set up the nine hospital study and got it running. We had a little breathing room and the next thing was the ECDEU program. It went quite nicely, as Henry Brill, Deputy Commissioner of New York State had already created a number of research units in state hospitals. Sidney Merlis was already at Central Islip and George Simpson at Rockland State.

TB: George Simpson was already working with Nate Kline and I think Don Gallant in New Orleans with Bob Heath.

JC: Heath was a remarkable man. He went from Columbia to Tulane so he could put wires in people’s brains, things they probably wouldn’t let him do in New York. He was clearly interested in neuropsychiatry and especially what the pathology was in schizophrenia. He trained excellent
psychiatrists, who now staff the Louisiana State Hospital system. So, he ran a good clinical program, trained excellent people, while doing his oddball research. I think he was deceived by his research assistants; they kept recording figures that didn’t quite work out. People went down to site visit and they couldn’t find the data. It was all very strange. My guess was that he was so charismatic that his research assistants found things to please him. It all fell apart, under scrutiny. But, Don Gallant, the guy who came in with him did very nice work.

TB: You also had Pierre Deniker in the ECDEU group.

JC: From St. Anne’s in Paris. We got permission for a few foreign grants including David Wheatley’s. He was doing studies with general practitioners in the UK. There was a major convulsion at NIMH when it turned out that Dave Wheatley’s was a for profit foundation. I can’t remember how we resolved that. I think we finally stopped the grant. For three or four years, we were funding him, assuming he was non-profit.

TB: The ECDEU program was certainly growing very fast. Would you like to say something about other studies and activities of the Center?

JC: We tried a study in outpatient anxiety and did a series of small studies, mainly at Hopkins and with Karl Rickels in Pennsylvania giving chlordiazepoxide (Librium) to anxious outpatients. Someone had the idea that if you gave patients a drug which caused noticeable side effects it would have therapeutic effects. It turned out that it worked exactly the opposite way. Rickels worked with medically ill people who were dumped on psychiatry by medical outpatient clinics and when he gave them a dry mouth on top of their troubles they thought that was a major imposition.

TB: Then you did a collaborative study in depression?

JC: We did a seven hospital study of inpatient treatment of depression. They were patients who’d failed on tricyclics as outpatients so I expected to find, if they took tricyclics as inpatients, they might do differently. We really had to analyze the data in various fancy ways to even show that imipramine was different from placebo. By only taking the worst half of the patients we could show that it was. We opted for a dosing regimen, where the dose went up to about the fourth week and then came down in the sixth week. We didn’t yet understand you ought to get the dose up and stay there for awhile. And we’d gone wild on metrics. We had about twelve different rating scales we factor analyzed. By the time we got to that point, I think, we had data poisoning. The findings of our study were published, but it was not a great success.

TB: You said that there were many rating scales used.

JC: We had the BPRS and several other scales including one that Al Raskin developed. I can’t remember the scales we used anymore. We accepted
anybody for that study who was depressed psychotic or not, we didn’t discriminate. Some of the findings were sensible, e.g., that agitated patients got better on chlorpromazine whereas unagitated patients got lethargic. And only in the sicker half of the patients, in the more endogenous non-alcoholic patients, could we pick up an effect.

TB: So, findings were not spectacular.

JC: Weren’t spectacular. Then, Bob Prien joined us and he was running a lithium vs. chlorpromazine study in bipolar patients; that worked out quite nicely in retrospect.

TB: When did Bob Prien get into the picture?

JC: Around 1960. He was a psychologist who was working for the drug company, Lakeside. He came to work for Ron Bonato at George Washington in the Biometric Laboratory and we ran the lithium, chlorpromazine comparison in bipolar patients.

TB: Is there anything else you would like to add?

JC: Marty Katz and I did a study with LSD in prisoners at an institution in Maryland where they send violent people.

TB: Then, in the mid-1960s you left NIMH?

JC: In 1967 two things happened that blew me out of the NIMH. They turned down the offer of St’.Elizabeths’ to give me a research ward. If I had been given the research ward or the responsibility for research on drug addiction, I would have stayed.

TB: Where did you go?

JC: I accepted the position of Medical Superintendant at Boston State Hospital and spent a fascinating five years learning all about community mental health and open door policy.

TB: Those were the years of deinstitutionalization.

JC: We were doing quite well with our discharged patients, so it was not a bad program. I was convinced that for some patients the hospital was a better place than the nursing home to get help. I played for awhile with the idea of how you could measure quality of life in nursing home and hospital inpatients who, wherever they were, said everything was fine because they hated change more than anything. I would rather have kept the hospital going even if they wanted to close down hospitals. I would rather close other places and transfer more patients to us to take care of. We closed our medical research facility and started using the public health hospital instead.

TB: What would you have done actually if you had your way?

JC: I would have stopped discharging patients. I would have liked to think about, who we wanted to admit and who we wanted to discharge. I
would have liked to decide who we could help. That's the crucial question we never found an answer to.

TB: I see.

JC: I began to feel that my flexible administrative style plus the lack of any liability insurance for my deeds as Superintendent were going to get me into trouble sooner or later. The business manager of the hospital used to complain that we fed twice as many people at lunch time than we did any other time of the day. A lot of our discharged patients would come back and mix with the current patients and eat lunch in the hospital. I began to have cardiac symptoms, probably psychosomatic, and decided to take the Chairmanship of Psychiatry at Temple University in Philadelphia for a year.

TB: So you went to Philadelphia.

JC: For a year, but by the end of the year Temple did not look as good and I was offered a job at McLean's back in Boston.

TB: You are still at McLean. Are you still active?

JC: I am seeing depressed patients and occasionally other patients, in consultation.

TB: We have to wrap it up now but I have one more question. While you directed the Psychopharmacology Service Center you were in a position to influence the development of the field. Did the field move in the direction you would have liked to see?

JC: I would have liked to see that clinicians and basic scientists getting closer, to see some kind of closing the gap between them. I'd always felt both, clinicians and basic scientists should be supported. I was always worried that the basic scientists were studying A, while clinicians were observing B. I think we have made some progress in that direction. I am impressed that people like Steve Hyman, who directs NIMH currently, have a good command of both ends of the spectrum.

TB: So, you seem to be pleased to see what is taking place. On this note, we conclude this interview with Jonathan Cole. Thank you very much Jon, for coming to Nashville for this interview.

JC: Thank you Tom for helping me. Thank you, Oakley Ray for asking me to be interviewed again.

TB: Well, thank you for answering all these questions.
DH: Today is the 8th of December, 2008. This is the ACNP Annual General Meeting in Phoenix, Arizona and I’m David Healy, here to interview Max Fink.

MF: Good morning.

DH: Can we begin with where you were born and how you ultimately went into medicine?

MF: I was born in Vienna on January 16, 1923. My father was a medical student who had just finished his training. My mother was also a medical student whose training was interrupted by her pregnancy with me. Soon after I was born, my father came to America for an internship. My mother and I lived in Vienna and a year later we immigrated to New York. My schooling was in an elementary school, PS 77, in the Bronx and then, high school, James Monroe HS, nearby; both within walking distance from our apartment just above my father’s office. He was a general practitioner serving a community of working families, caring for them from birth to death. He had special training in radiology in Vienna and had an x-ray in one room of his office. He also had an early electrocardiograph and a busy clinical laboratory. As a teen-ager, I was often called to develop films, help in setting fractures, and do simple laboratory tests of urine and blood. I always assumed that I would follow him in medicine, even knowing that admission to medical school was very difficult as a Jew. I finished elementary and high school early, graduating at 16 in January, 1939. I enrolled in New York University at their University Heights campus, graduating in June 1942, after three years of college. I was admitted to New York University’s School of Medicine on December 6, 1941, the day before Pearl Harbor. With the war the government took over and I became a soldier, Private First Class; so my medical school training was under military auspices. When I graduated on June 12, 1945 I received both my MD degree and my appointment as First Lieutenant in the Army Medical Corps.

My medical school training was a very interesting experience because few trained physicians were available to teach. At Bellevue Hospital I was taught by women and older physicians who were not called to military duty. Bellevue Hospital had its own army hospital in Europe and all our leading professors were over there. As a consequence, I learned to be an “interventionist”. I like that word, because I dealt with maggots.
and osteomyelitis, blood samples, spinal taps, including cervical 4th ventricular taps in people with neurosyphilis.

My internship at New York City’s Morrisania Hospital was equally interesting because I participated in an experiment. I worked on a pulmonary medicine ward that had about twenty patients with empyema. To treat empyema in those days one took a trocar, pushed it into the chest, pulled out the pus, put in saline two or three times until clear fluid came back. This was done every day or every other, day. The clinician in charge, Dr. Eli Rubin, was carrying out an experiment, injecting either a known sulphonamide antibiotic or an unknown new agent “Compound X”. The unknown agent was so precious that it was kept in a safe in the director’s office. I was responsible for assigning each new patient to one treatment or the other; the even numbered patients would get one treatment, the odd numbered, the other. Within two weeks, it was obvious that patients who received the new drug were doing considerably better; the fluid was thinner, the appetite was better, the fever less. It was one of the first experiments with penicillin. We had an interesting time when a young Puerto Rican woman came in with her baby. When her assignment was to sulphonamide, contrary to law and rules, I switched her to compound X. Maybe a week later, the physician in charge, sees the numbers and says, “This is remarkable; hmm, she’s doing very, very well. She shouldn’t be, right? What did you do? How did you treat her?” And, he took a look at the number and he took a look at what I had done and he said, “You broke the code.” I was in tears. I was taken down to the director’s office and the director said, “Well, you’re suspended; you didn’t obey orders”. I didn’t know what to do. I called my father and told him the story. He called the Director and negotiated a better resolution; I believe I lost my salary for the month, probably $25.00.

My residencies were also interventionist. The first was at Montefiore Hospital and as a new neurology resident I was the youngest and the most junior member on the service. The neurosurgeon was Leo Davidoff, who had been superbly trained; he had an international reputation and patients came to see him from all of the Americas. He practiced percutaneous carotid angiography and the neurosurgery residents taught me how to find the carotid artery, introduce the needle, take out the stylet, put in the syringe, inject the radioopaque dye and obtain three immediate x-ray pictures. It was a great experience. My next residency was at Bellevue in neurology. On neurology rounds I see a patient for whom an angiogram would be useful, and request it. The director says that it is not available. I explain that it is simple to do and Professor E. D. Friedman suggests I work out the details with the radiologists. With a fellow resident, Joseph
Stein, we negotiate the x-ray agreement and build a box to hold the three x-ray plates. Our first patient had a subdural hematoma and the anterior-posterior view on the angiogram showed the blood vessels nicely pushed aside. From then on Joe Stein and I did a hundred and five angiograms and published two papers on carotid angiography. This interventionist experience was a strong basis for my interest later in EEG.

DH: How did you move from there to the mental health field?

MF: While I was at Bellevue, I had two well-known teachers. One was Bernard Dattner, a student of Wagner-Jauregg, the 1927 Nobel Prize winner in Medicine for work on fever therapy in neurosyphilis. Dattner was a Jew who had left Vienna for America because of the Holocaust to join the NYU faculty. I was a student with him in 1944. He ran the neurosyphilis clinic and taught me how to do fourth ventricular taps. That was an intervention where patients lie on their left side, bend their neck forward with chin on their chest, and the doctor puts a needle between the vertebrae to withdraw spinal fluid from the 4th ventricle. It took me awhile to realize that if I went another inch, I would be pithing a human, but Dattner said, “Don’t worry, you’ve got plenty of space”. So I collected CSF for a couple of months. He also taught me a lot about fever therapy and the colloidal gold test for neurosyphilis. We treated patients in fever boxes, sweating them for hours; my job was to monitor fluid intake and body temperature.

At the same time, I was taught also by Morris Bender. He became the chairman of neurology at Mt. Sinai Hospital and was, for many years, president of leading organizations in neurology. Bender was interested in sensory stimulation and physiology.

While in the Navy, he had a patient with a lesion in the parietal lobe. As he was doing sensory tests he found that, when two stimuli were applied in the visual or the somatosensory field, the patient would appreciate only one stimulus; the other was “extinguished”. Extinction was demonstrated in visual field tests on patients with occipital lobe lesions. Bender put me and other residents, Martin A. Green and Joseph Jaffe, to work in double simultaneous cutaneous sensory stimulation tests. My first research papers, a whole series, described the Face Hand Test, Double Simultaneous Stimulation in Patients (DSS) with Mental Deficiency and the use of the tests in children. The most interesting study was development of a test for the “organic mental syndrome.” Patients with diffuse brain disease made errors of extinction and displacement on simultaneous stimulation. If the patient seemed to have a brain lesion and the simple DSS test was ambiguous, we gave intravenous amobarbital, and the double simultaneous extinction phenomena became obvious. We published this clinical test which is still recommended for detection of a
“soft” neurological sign. At one point, we thought of applying the test to patients getting insulin coma or electroshock.

Bender suggested I obtain an appointment at Hillside Hospital, a sister Federation institution on Long Island, dedicated to psychiatry that had a new residency program. I hadn’t intended to take another year of residency but I visited the hospital and I was very pleased with what they offered me, which was residency for a year, focused on psychodynamic psychotherapy. It began in January 1952. I had already become interested in psychoanalysis by attending classes at the William Alanson White Institute during my neurology residencies.

I joined Hillside Hospital on January 2, 1952, and my first assignment was to the ECT service. ECT was given three days a week and, at the same time, the resident supervised the adjoining insulin coma therapy (ICT) unit. Never having seen ICT and never having given ECT I was the student assigned to do it. The Attending Psychiatrist, Simon Kwalwasser, taught me how to administer ECT and walked me through ICT for two or three days and then said, “You’re in charge of both ECT and ICT”. I was perfectly happy to be in charge of 22 beds for patients in insulin coma every morning, five days a week, and giving eight to ten patients ECT. The patients received insulin injections from nurses at 6:00 am. When I came in at 7:30 or 8:00 am the patients were already stuporous. At about 9:00 or 10:00 in the morning we tested whether they were in coma and wrote the time on a chalkboard at the foot of the bed. Sixty minutes later, the nurses called me to administer glucose either by gavage or intravenously. It was a remarkable experience to see a patient in deep stage IV coma, without pupillary or deep tendon reflexes and unresponsive to pain, speak within 15 minutes and become fully oriented. I spent the afternoons doing psychotherapy under the supervision of accredited New York psychoanalytic psychiatrists.

While in the Army I was assigned to a field aid station in a company of the 2nd Infantry Regiment. One day I was called to headquarters and given orders to attend the Army’s School of Military Neuropsychiatry at Fort Sam Houston. To this day, I have no idea why I was selected. I attended the school for four months; one-third the course was training in psychoanalysis, one-third in general psychiatry, and one-third neurology. One of the teachers was Gilbert Glaser, the Neurology Chairman at Yale for many years. We learned a great deal. In my group were three or four doctors interested in psychoanalysis. I look back and wonder how did that come about, but the reality was that everyone at that time thought psychoanalysis was the future of psychiatry. Indeed, when I was in neurological training at Bellevue, I decided to attend an analytic school at the
same time. I was aware of the philosophical barrier among neurologists for psychoanalysis. If I had gone to Morris Bender, E. D. Friedman or Bernhard Dattner and said, “I’m going to go to psychoanalytic school”, I believe I would have been asked, nicely, to take another residency elsewhere. At the time, there was much rivalry and antipathy between the fields. I had visited different analytic schools in New York and one, the William Alanson White Institute, accommodated residents in training with courses given in the evenings and Saturday mornings. One course was in Washington, DC. I would travel by train on Friday night, stay overnight, take a course for a whole day on Saturday with Dr. David McKenzie Rioch and then I would return. I also became acquainted with his wife, Janet Rioch. It was a very intensive course and I graduated in 1953 with a Certificate of Psychoanalysis for Physicians. I also went through four and a half years of personal analysis. In retrospect, it was neither helpful nor harmful; it was quite benign. My analyst, Joseph S. Miller, was very reassuring. My recollection is that I would go three or four times a week, all paid for by the United States government under the G.I. bill. The most fascinating part was that, when I opened my office in 1953 for neurology and psychiatry, I did psychotherapy for a while. I found it boring to sit and listen to somebody talk for forty minutes during the day when, later that evening, I would go into the next room and induce a seizure in an ECT treatment. After three weeks, the ECT treated patients were better and the psychotherapy patients kept coming back and back but I didn’t know how to get them better. This was in the days before we had imipramine or chlorpromazine.

DH: Before we leave the issue of insulin coma, can you walk me through that?

MF: That’s another fascinating experience. Insulin coma was a creation of Manfred Sakel, who was Viennese. He had first learned about insulin as a new treatment for diabetes. Insulin was discovered in 1922. In 1928, Sakel was in a hospital in Berlin where he was treating patients with drug addiction, many in opiate withdrawal. They lost weight, vomited, sweated a lot. He decided to give them insulin in order to improve their appetite. After insulin injections the patients calmed down. Next, he went to the University of Vienna where he continued his experiments with insulin and found that these patients would also calm down after insulin. In retrospect, it was probably the patients who were catatonic and depressed that seemed to improve. The definition of schizophrenia in those days was not very specific; it was quite broad and included catatonia as a type of schizophrenia. Every psychotic patient was considered schizophrenic. Insulin coma came to the United States in the late 1930s and Hillside Hospital, where I took my residency, offered the treatment early on.
DH: What year was insulin coma introduced at Hillside?

MF: I think the first time we have records was in 1937 for insulin coma, Metrazol (pentylenetetrazol seizures the same year, and ECT probably by 1940. I am not sure. When I took over the unit in 1952 we offered patients up to fifty insulin comas; the procedure had been well developed and there was a worldwide interest in it. Some doctors offered forty comas; some thirty and some did sub-coma insulin. Every variety of treatment and dosing was tested and reported. My study of ICT was in 1956. I had already introduced chlorpromazine (Thorazine) to Hillside. It was obviously effective in the same patients that we referred to ICT, so I considered a random assignment study. Because it was a psychodynamic hospital, the residents and the attending physicians paid little attention to ECT or ICT. When they sent the patient for ICT or ECT that ended their interest. My unit was a dumping ground where they sent all the older, severely depressed, severely psychotic, and manic patients. We did this random assignment study in 52 patients, 26 with ICT and 26 with chlorpromazine. Chlorpromazine and ICT were equally effective or equally ineffective because there was about a fifty percent response rate. We didn’t go by remission in those days, we went by dischargeability; was the patient well enough to leave the hospital? The results for the two treatments were the same but chlorpromazine was less expensive, did not require four or five hours of nursing care every day, and the risks were much less. My unit had eight or nine nurses for twenty-two patients; it was very labor intensive. When I presented this material to the Attending physicians, they were favorably impressed. I offered to close the insulin coma unit and they agreed. We published the paper in JAMA in 1958, and it was well received; I still think it’s one of the better papers I’ve done. It was a random assignment study but we were not blinded. That’s the main its limitation, but we did measure the results by the discharge rate, the rating scales and the fact that by the time the study was over, every nurse in the hospital was sending me patients for chlorpromazine. When I arrived on my morning rounds the nurses would walk up to me and say, “Dr. Fink, please see Mr. so and so in my ward”. The residents weren’t interested initially but eventually began to refer patients for chlorpromazine; that ended insulin coma at Hillside and eventually at other hospitals. Many years later, there was a very famous economist, John Nash who stimulated interest in insulin coma again.

DH: He was famous for game theory.

MF: Right. John Nash of Princeton eventually received the Nobel Prize in 1994 but soon after he published the research that led to the award he became severely psychotic. He had gone to Boston as a Lecturer and was...
admitted to McLean Hospital where they kept him in psychotherapy for a couple of weeks. As he tells the story, he figured out what they wanted from him, hid his symptoms and they let him go home. He returned to Princeton but relapsed and was admitted to the local state hospital. The best unit in 1961 at a State hospital was the insulin coma unit, with the most nursing care, best food, best qualified doctors. He was treated and recovered dramatically but it didn’t carry over because he refused to take the prescribed chlorpromazine and eventually relapsed. The story was told in a fine biography on which a film was based and produced about seven or eight years ago.

DH: It was called *A Beautiful Mind*.

MF: *A Beautiful Mind*, thank you. I received a phone call one afternoon from the author of the book, Sylvia Nasar, “Are you the man who did insulin coma at one time?” she asked. “I’ve been given your name by the National Institute of Mental Health. I’ve written this book and we are going to make a film from it, would you be willing to be a consultant”? I had read the book, so, I was pleased to agree. If you look at the credits, I’m the last one, well, not quite; there are two after me. So, I had to tell my friends, please stay to the end!

DH: Did you meet any of the big names in the insulin field, like Manfred Sakel?

MF: I met him, I think, twice. He had been at meetings in the United States, but I did not have any personal relationship with him. I did, however, have a very close relationship with his cousin. When I was an intern at Morrisania City Hospital one of the neurology attendings, a very young man, was William Karliner. When I was at Hillside in 1952, Karliner was also a member of the attending staff and he stopped by the ECT unit a number of times. Together we examined different electrode placements. He would fiddle with the placements long before it became fashionable. It was already known in 1952 that unilateral ECT was different; you could produce a unilateral seizure if you were very careful with the current. Over the next few decades I got to know him well and I’m still in touch with his wife. He died a few years ago. Karliner was Sakel’s cousin and described him as rather egotistical, not at all collaborative. Sakel made a lot of money as a physician, which was unusual in those times. He had insulin coma patients who were wealthy and he set up a foundation. Karliner gave me a different image of the man. In the electroshock world I came to know many of the people who were the leaders.

DH: Can we begin to pick up the psychotropic theme? You were involved in some key early trials for chlorpromazine. How did you get to hear about chlorpromazine?
MF: Two years before chlorpromazine, in 1952 at Hillside, I heard about LSD and there were suggestions that an LSD experience was an “open road to the unconscious”. LSD offered subjects images and strange thoughts that many believed were expressions from their unconscious. I obtained LSD from Sandoz and recorded the EEG of patients taking LSD. I offered LSD to any psychiatry resident provided they took it in the EEG laboratory under supervision of my team; they would write notes during the experience and share them with their attending. It was very popular; almost every resident volunteered!

One day, the director of the hospital, Joseph S.A. Miller, handed me an announcement of a symposium on chlorpromazine at Creedmoor Hospital, a State hospital nearby. It was an all day affair, organized by Henry Brill, who was Commissioner of Mental Health for the State of New York. They had received chlorpromazine six months earlier, and had put it experimentally in state hospital. That day I heard Nathan Kline, Herman Denber, Tony Sainz, Sidney Malitz and Sidney Merlis, each a leading figure in psychopharmacology in the late 1950’s, presenting their experience. It was a fascinating day with every speaker telling stories of how patients calmed down and were more manageable. At the end of the day, I went to the back of the conference room, met the representatives of Smith, Kline and French, signed a card and requested samples. They sent me one or two hundred tablets and the next day I gave it to patients with psychosis. Within two weeks a nurse asked me to see a patient who was grossly psychotic and to give the patient the drug. We didn’t advertise “chlorpromazine”, instead we had a code number. I agreed but asked the resident to approve, who replied, “Thank God, yes; I’m not capable of psychotherapy with this patient”.

Almost every patient I wanted to treat at Hillside for the ten years I was there was available to me for study. About the nurse and her referral, my father said, “You’ve got something special there; don’t stop; whatever you do, that’s a very special something”. “Why?” I asked. “Well, nurses are the only ones who observe patients closely”, he replied. So chlorpromazine was introduced through this one-day symposium and the willingness of Smith, Kline and French to supply the drug.

A few years later, Donald Klein joined me at Hillside Hospital. We set up an RCT study. We had already studied imipramine by EEG and clinically and had some ideas that imipramine and chlorpromazine were different classes of drugs. We were particularly interested in the fact that the two drugs had different EEG patterns and different effects on behavior and neuropsychological tests. Don, I and the psychologists, Robert L. Kahn and Max Pollack had a team meeting and decided the only way to
do an EEG and behavior study properly, was by random assignment. We devised a very simple study; every patient referred to us for medication was randomly assigned to treatment with chlorpromazine, imipramine or placebo. The residents could refer patients “for medicine” but could not refer them for a specific drug and they were happy. I keep emphasizing the uniqueness of the environment where almost anything we wanted to do was welcome. The study was designed with EEG monitoring and rating scales. At that time we had the Lorr behavior rating scale and, I think, the Brief Psychiatric Rating Scale (BPRS) of Overall and Gorham. This was before the Hamilton Depression Rating Scale. Over a two-year period, we studied 144 patients; one third received chlorpromazine, one third imipramine and one third placebo. For six weeks every patient received liquid dosing three times a day: 10, 10, and 20 cc. The concentrations were made up so that imipramine dosages were 75, 150, 225, or 300 mg a day; Thorazine doses were 300, 600, 900, and 1200 mg a day and placebo was vehicle only. Both, Geigy and Smith, Kline and French were delighted to give us the chemicals, and it was Smith, Kline and French who gave us the vehicle in which the chemicals were dissolved. For chlorpromazine we added Kemadrin (procyclidine) as an anti-Parkinson agent to mask the extrapyramidal effect of chlorpromazine. The masking was quite good; Don Klein asked every resident to guess which drug their patient received. A small number of patients who had placebo got better and the doctors assumed it was either chlorpromazine or imipramine. Many patients on chlorpromazine thought to be on imipramine and many patients on imipramine thought to be on chlorpromazine. We published our findings in a series of papers over the next few years. Don Klein went on to replicate the study, with the same findings, which is remarkable. I left Hillside in 1962 and Klein went to Columbia University and the New York State Psychiatric Institute where he continued psychopharmacology research.

DH: What were the results of the individual drugs?

MF: Chlorpromazine was a very effective sedating agent for patients with psychosis. It also was a very effective antidepressant for patients who were severely depressed; probably the psychotic depressed. Imipramine had a very good effect on depressed patients. It also had, in young adults, an exciting effect, so we had I think, three or four patients who went into manic states. The placebo had some benefit to some patients, as one would expect, but it was significantly less effective than either of the two drugs. So, we published papers on chlorpromazine as an antipsychotic, imipramine as an antidepressant and chlorpromazine as an antidepressant. The paper, on the antidepressant effect of an antipsychotic was
published in 1962. It was the second paper on the antidepressant effect of an antipsychotic. The other paper was by Leo Hollister with a different antipsychotic as an antidepressant. I’m not sure which one. That issue of an antipsychotic as an antidepressant has plagued the field for many years and was explained after 1975 when Alexander, Sandy Glassman showed that psychotic depressed people don’t respond to imipramine, but do well with an antipsychotic and antidepressant in combination, or, even better, with ECT. In his report, 13 patients who had not responded to imipramine and failed whatever else given, when referred to ECT 12 of 13 remitted. That was the fundamental paper showing that psychotic depression is a distinct entity in the depression spectrum. Since then psychotic depression has been a primary indication for ECT.

DH: It’s also worth mentioning, this was the trial that gave rise to Don Klein’s idea that there’s a condition called panic disorder.

MF: Yes. As I remember it was a group of young women who wore raincoats. They were severely phobic, and imipramine did resolve the phobia in some of them. That was another paper that was written from our research. Klein went on to study the issue of panic disorder by a different route. I don’t think it was from our studies.

In 1969, I had two outstanding residents at New York Medical College. One, Richard Abrams went on to write about ECT, while the second, Michael Taylor, worked closely with me on catatonia and melancholia. Abrams and Taylor wrote the first important papers on catatonia outside of schizophrenia. They reported catatonia in mania in 1976.

Back to Klein and panic disorder. In 1969, I read a report by Pitts and McClure at Washington University on Lactate Infusion stimulating anxiety disorders. Michael Taylor was my resident at the time and I handed him the paper and I said, “Let’s find out if this is true”. We went to St. Louis and met Pitts and McClure, saw what they did, and wrote a protocol. We asked Pitts to ship us fluid for lactate infusion that he had used and we did an exact replication. We took panic disorder patients and their spouses or siblings, gave both lactate infusions, and confirmed their study very nicely. It was one of those situations, “Do you publish a confirmation, and if so how”? So, we published a letter and simply said, “Pitts and McClure are right”. Taylor applied to NIMH for a grant, and the grant was awarded but at the same time the United States Navy called him to service and he left. I didn’t have anybody to take over the grant. One day, Don Klein asked if I would be offended if he took the Taylor protocol and completed it. My attitude was I couldn’t do it, so why not. By that time, I was interested in something else.
In my lifetime I’ve had a number of research fellows to whom I’ve suggested studies. One year, read about the dexamethasone suppression test (DST) by Bernard Carroll. I had a fellow from Greece working with me at Stony Brook, Yiannis Papakostos. I asked him to find out if it was true. I helped him design a protocol and get it through the appropriate hospital authorities. Eventually we were able to describe the dexamethasone suppression test in patients before and after ECT. Before treatment it is abnormal; afterwards it’s normal and when it’s abnormal again the patient has relapsed. So we felt Carroll was correct. That kind of experimentation is part of my history; there were a number of similar studies.

DH: Before we leave the drugs completely you also produced probably the first report about people having withdrawal problems from antidepressants.

MF: Yes. We were treating the patients at Hillside with imipramine, chlorpromazine, and other drugs, and, of course, we didn’t know what to do at the end of a trial. After six weeks treatment, we stopped the medication. There was no reason not to, whether the patient improved or not, since we did not have experience with long-term dosing. This was 1959 or 1960. I had a resident, John Kramer at the time, who told me about a patient who, he thought, had an upper respiratory problem but the internist found no infection. Her nose was running, she had back pain and had quit eating. Then another patient, and then a third had the same symptoms. I told Dr. Kramer to see every patient right after treatment stopped. He saw these “withdrawal” symptoms after chlorpromazine and imipramine and put together a paper with Don Klein on withdrawal symptoms to imipramine. It was published in the American Journal of Psychiatry in 1961. It was amazing, nobody had ever seen it or heard about it, but we did the definitive experiment, raising the dose to three hundred milligrams and then stopping; forty-eight hours to seventy-two hours later, patients had withdrawal phenomena which we described. It was a rewarding experience.

DH: When did you commence to use the EEG as a tool to look at what drugs were doing?

MF: I’m not sure of the first experiences, but at Bellevue I used to order EEG’s as a resident as a test for epilepsy. This was between 1948 and 1951. A treatment for epilepsy with phenytoin had been developed, I think in 1938. If you made a diagnosis of epilepsy on the EEG and behavior you could treat the patient. But more interesting was insulin coma. I’d already learned about EEG changes in frequency from alert to sleepy, to deep sleep, to stupor and coma. When I went to Hillside, it did not have an EEG. I applied for a Fellowship from the National Foundation for Infantile
Paralysis and went to Mt. Sinai Hospital two days a week for a year to learn EEG with Hans Strauss who had published a textbook on EEG practice. I still worked at Hillside and after I was trained the hospital bought a Grass EEG instrument.

That purchase was a wonderful little story. The director Joseph S.A. Miller asked, “How much does it cost?” I replied, “Well, it’s five thousand dollars”. That was, a lot of money in those days. A few days later, I got a message to come to his office and he handed me a check for five thousand dollars, a grant from the Dazian Foundation. The hospital bought a Grass electroencephalograph, hired a young woman who I trained, and we started doing EEG’s on everybody. We recorded the EEG during insulin coma. That’s easy, but when I tried to do it during an ECT seizure I burned out parts of my instrument and had to have them replaced. I could record 24 hours later an inter-seizure EEG. That was the way I started to study the mechanism of ECT’s action.

We set up a schedule of experiments so that an EEG was recorded a day after a treatment each week. We had records of patients who had 1 to 3, 4 to 6, 7 to 9, and 10 to 12 seizures. On the average, we gave twelve treatments. We didn’t know why but nowadays, worldwide, depressed patients need six to seven treatments to achieve remission.

Using the same design we studied the effects of chlorpromazine and imipramine using 1200 mg of chlorpromazine and 300 mg of imipramine because these dosages were effective in 80% of the patients. We next studied the effect of amobarbital on the EEG. We showed that amobarbital changes the EEG effects of electroshock; if a patient has had three treatments and you give them amobarbital it looks like they’ve had six or nine treatments. We used to measure the EEG by hand with a ruler scoring the amplitude and width of the waves. The width was expressed quantitatively as cycles per second. We examined six 10-second samples, to quantify 1-minute epochs. It became obvious in the first work we did that the EEG reflected brain function very, very dramatically; momentarily, and it was sensitive to changes in the patient. If a patient has an EEG running and I gave LSD, within three minutes we saw changes. You see the effects of amobarbital within a minute. Years later, when I did the first EEG measures of benzodiazepines, within a few cardiac cycles the EEG was showing induced fast waves. It’s almost instantaneous; a most dramatic effect. This work formed the basis for two lines of subsequent research. One was my studies of EEG and electroconvulsive therapy and the second was my interest in quantifying the EEG. I became tired of hand measurements, and sought ways of doing it electronically. A report published in 1957 or 1956 described an electronic frequency analyzer developed.
in St. Louis by George Ulett, then Professor of Psychiatry at Washington University. I was impressed by his demonstration. George said he had all the material to build a frequency analyzer for me. I applied to NIMH for funding and it was awarded. He shipped the analyzer to Hillside Hospital and we were one of the first to apply a frequency analyzer for pharmaco-EEG studies in about 1958. That was also why I moved to St. Louis in 1962. George Ulett had been asked by the governor of Missouri, who had a crisis in his mental health system, to become Director of the Office of Mental Health. They had found that the nurses and aides were offering women patients for sex to outsiders, acting as pimps. After the governor fired the Mental Health director Ulett took over with the proviso that he could create an Institute for Research and he offered me an appointment as Director of the Institute. In 1962, I was also appointed research professor at Washington University and spent four years in St. Louis.

DH: Could you take me over the research you did after you moved to St. Louis?

MF: I'm going to go back a bit, because it was at the time I was working at Hillside that we began evaluating new drugs. Once the system had been set up for chlorpromazine and imipramine, every new psychotropic drug that came to Hillside was examined. In 1959, I was invited by Jonathan Cole to be part of the Clinical Drug Evaluation Committee of NIMH. That Committee set up what were called Early Clinical Drug Evaluation Units, ECDEU. We met a few times a year as investigators and as a grant-reviewing organization. Dr. Cole had fifteen million dollars that we assigned to investigators around the country to study the new drugs. This was 1959 or 1960. One of the grant awards went to Hillside. The people on the committee were the people who'd done the work in the previous four or five years on drugs and each investigator were asked which aspect of psychopharmacology they were willing to study. Herman Denber, at Manhattan State Hospital, was a psychoanalyst as well as a psychopharmacologist and interested in the effects of drugs on the unconscious behavior of patients in groups. Some units were doing urine chemistry, so there were studies on the metabolites of chlorpromazine. I was interested in EEG and the first grant I had received was NIMH Grant M-927 for the study on the EEG effects of electroshock in 1954. The next grants were for pharmaco-EEG trials, although we didn’t call it that. It was the effect of different drugs on the quantitative electroencephalogram.

In 1958 in Rome, at one of the early meetings of what became the CINP, my interest was matched by that of a group from Erlangen, Germany. I presented a report on the acute and chronic EEG effects of imipramine, chlorpromazine, and placebo. Imipramine and chlorpromazine showed
EEG effects that differ from those of ECT. I was on a panel with presentations by Turan Itil who collaborated with Dieter Bente. Their paper was also on the EEG effects of chlorpromazine and imipramine. Their findings and mine matched. Afterwards, we got together and it was obvious that my slides and his were identical; it was amazing that in Germany and America we had the same findings. This technology separated the effects of two active psychotropic drugs. We hadn’t finished the three drug study with Klein, but it was important that this was shown. We also knew at that time that other drugs had different EEG effects and for the next two or three decades the issue was “What can be learned from the EEG changes induced acutely and chronically”? That became the science of pharmaco-EEG.

In 1961, Itil wrote to me saying he would like to come and work with me in New York if I had the money. I said I did, but by the time he was ready to come, I had moved to St. Louis. Over the years he and his wife told me they hadn’t known where St. Louis was. He came due to his interest and enthusiasm in pharmaco-EEG and because I had the equipment he lacked in Germany. In St. Louis, one of the first things I did was work with Washington University to develop a digital computer analysis of the EEG.

The first digital computer analysis of an EEG signal was presented in 1960 at UCLA at the opening of the Brain Research Institute. I was invited to attend and I brought back with me a strip with the quantitative energy scores of different frequency bands. I told Dr. Ulett that we should seek a digital computer analysis instead of the electronic frequency analysis. The work had been done at MIT and eventually we were one of the centers that started a digital computer analysis of EEG.

Our first digital computer was an IBM 1710, with key-punch and card reader for Hollerith cards. The memory was very small, but eventually we graduated to an IBM 1800, a much larger computer with more memory. From the first day that we conceived of this method of quantification the Federal government, the State of Missouri, and the State of New York gave me the money I asked for. It is phenomenal to realize that when I moved back to New York in 1966, I went to NIMH requesting $1.2 million dollars for this computer. I next received a letter saying if I was doing studies on psychotropic drugs could I also do some studies on drugs of abuse? Fortunately I was studying opiates so they gave me $1.2 million dollars for the equipment as well as annual support for personnel until 1975.

The importance of pharmaco-EEG was multiple. The first was that you could tell whether a drug was active or not on the brain, wheter it got
through the blood-brain barrier. If it doesn’t have an effect on the brain, it’s not going to have an effect on behavior. That syllogism, that psycho-
tropic drugs must first have an effect on the brain to have an effect on 
behavior, is still true and much ignored today. Sadly, no direct measure-
ments of brain function are made to be sure that the drug has such an 
effect in humans.

Pharmacologists also argue that if an agent does have an effect on 
the cat, mouse or rat it must do the same in man. That syllogism is not 
true. We examined drugs that were active in the dog or in the mouse 
and rat that are not active in humans at the doses given, e.g., flutroline. 
The EEG differentiates the effects of the compounds; chlorpromazine 
from imipramine; imipramine from LSD and atropine from LSD. Atropine 
and imipramine are close, but we found differences. When the benzodi-
azepines became available they had a totally different profile. As Turan 
Itil has published, one can predict a drug’s psychoactive effect from EEG 
studies in man. He worked out a quadrant of four axes of EEG changes 
that are associated with the individual clinical effects of different drugs. 
When the EEG profile is on one pole, its clinical effects are of a particular 
class. Some drug profiles fall into several quadrants, offering different 
clinical effects in different doses and populations. If a drug is in both the 
antipsychotic and the antidepressant quadrants it’s going to have effects 
on some patients as an antipsychotic and on others as an antidepressant.

We can also demonstrate whether a drug is pharmacologically active 
or acts as a placebo. We did multiple trials at different dosages and found 
some drugs which at one dose would have a suggestive profile but at a 
higher dose had a clear profile. And in some at an even higher dose we 
saw yet another profile. From these data we could predict the effective 
clinical dose range. Remember, all of our work is in humans. It’s critically 
important to realize that the literature on EEG and drugs is split into ninety 
percent of work done in animals which is of little, if any, relevance to 
human psychopharmacology. Humans are a different species than rats, 
cats, dogs and definitely different from cats in their pharmacology. There 
was a wonderful symposium on EEG in animals and man at the Society of 
Biological Psychiatry about 1966. It is published as Anticholinergic Drugs 
in Animals and Man. edited by Philip Bradley and myself. In that book, 
there are articles on the effect of anticholinergic drugs in cats that differ 
from dogs, the monkey, and the mouse, all differing from the effects in 
humans. Man is different, so human pharmaco-EEG is a predictor of the 
clinical effects of psychoactive drugs.

DH: When all of this came out, how did the field respond, when you talk about 
humans but all these guys are working in rats, cats and dogs?
When I began to present the EEG profiles of humans at the American EEG Society, there were a series of papers that appeared from America’s leading pharmacologist at that time, Abraham Wikler, who was the expert on narcotics at the government Hospital in Lexington, Kentucky. He wrote a definitive text on pharmacology. Everybody used it and it went from hard cover to paperback. Wikler had done his work in dogs and at one meeting after another, would speak after me. He was much older than I and was very much respected. I was a young kid. He would say, “These findings are not at all what I see” and he would show his slides, and my data were ignored. It took awhile to realize that his work was in dogs, not humans. It’s very important because the pharmacologists believe with all their heart that animal trials are directly applicable to human studies. And a reason my work was disregarded was that I was much younger. Very few psychopharmacologists were doing human EEG work, other than Itil, Bente, Herrmann and a few others. We were a very small group. The Europeans, who were many more than the Americans, were not very assertive.

I visited Wikler’s laboratory and saw his experiment where the dogs are suspended on belly slings. The electrodes are implanted going through cable to an electroencephalograph. Wikler administers an anticholinergic to the dog and the dog’s legs are moving and the EEG is showing slow waves, but not showing the fast waves. Well, why didn’t they show them? Because the movement of the legs are inducing artifact, so it is very rare to get a clean EEG. In my opinion, he’s discarding the fast waves as artifacts. He’s discarding essential data he interprets as artifact. The conflict seemed to resolve in 1968 when we published that book with Bradley. It became clear that pharmaco-EEG was a human discipline if you’re going to be successful predicting drug effects in patients. Some in the pharmaceutical industry agreed, but then came the big issue of expense. Doing work in humans is not easy. Pfizer, to give them credit, had a relationship with a prison in Connecticut and asked would I be willing to set up an EEG laboratory so that their scientists could do pharmaco-EEG drug trials on prisoner volunteers. We set up the equipment, organized the recording protocols, and agreed to analyze the EEGs recorded on tape in New York. It was probably 1971 or 1972. Then Pfizer and all of the industry got a message that you can’t do experiments in prisoners; paying them was unethical as they were not free agents; so the laboratory was closed.

The same difficulty occurred in Holland in another way. I was doing studies with the Dutch at Organon. Itil also studied a number of their drugs. For each drug, we did the analyses in volunteers and in patients.
They realized they couldn’t do patient research in Holland, so they asked if we would set up an animal laboratory. I argued that they would have to use animals close to humans, possibly chimpanzees. They set up a laboratory with, I believe, six chimpanzees. They educated a team, implanted electrodes, and trained the animals. They had a cable setup with a large computer. We gave them the computer programs. The physical facility was magnificent. First, they planned some pilot work with established agents, probably imipramine or chlorpromazine, to see if the EEG’s were like humans. Yes, they were. I was very excited. However, one day I got a message that four of the chimps had died and they were now down to two. Are two enough, they asked? I don’t know, I replied. Chimpanzees die when they’re in a restrictive environment. I didn’t realize this. Eventually the laboratory was closed. They continued with some rodent studies but these led nowhere.

Then, the new game in psychopharmacology became chemistry. Electrophysiology was pushed into the background and, suddenly, everybody was involved with neurotransmitters.

DH: But you had picked out some drugs using your approach, hadn’t you?
MF: Two examples are important. One is a drug that Pfizer called flutroline, that the pharmacologists predicted would be “a one injection a week” drug, because a single dose blocked vomiting in dogs for a week. Human trials for safety were done and then clinical trials. First, I did an EEG study in human volunteers. I recorded the EEG profile at the dose they recommended, then at a higher dose, and then a dose which was far above what was accredited. None had an EEG effect. It just didn’t do anything. We next tested six patients at the Northport VA with a history of psychosis not responding well to standard antipsychotics. After having the protocol approved and the patients’ signed consent for a new drug treatment, we took them off their antipsychotic and replaced it with flutroline. In three weeks it was obvious that the drug, at the maximum dose I was allowed to give, had no antipsychotic effect. Experimentally, I increased the dose. It didn’t do anything. Pfizer didn’t accept it immediately. They set up additional clinical trials but, eventually, you have not heard of flutroline. We published the paper describing its potency in dogs and inactivity in humans in both EEG studies and clinical trials.

The other side of the coin was, of course, the experiment that was successful. On one visit to Organon they handed me documentation for testing the EEG profiles of six drugs. I could not handle six drugs in human trials at one time. I offered three files to Turan Itil who was in St. Louis with the same programs. His first was GB 94. I don’t know how long later, but I received a call from Turan that he was sending me some
GB 94 and would I do two subject trials. We did the paperwork, and then tested the samples in volunteers. I called Turan and I said, “This is very interesting; it’s exactly like imipramine”. He replied, “That’s what I found. I’m going to tell them in Holland”. Turan phoned, and we were invited to Oss in Holland. Itil presented his work and I presented my two cases and they said, “This drug has the pharmacology of drugs that affect migraine and we’re supposed to evaluate it for migraine”. But they agreed to study it as an antidepressant and I organized an antidepressant trial in New York. They also sent it to Hungary and Czechoslovakia and in time all the clinicians agreed that it worked like an antidepressant. It is called Mianserin, and Organon marketed it, but not in the United States. It would not have been marketed as an antidepressant if it hadn’t been for the pharmaco-EEG studies.

DH: It actually did well in Europe.

MF: A best seller.

DH: Yes, for most of the 1980’s. As I understand it, the reason it failed in the US was that they picked the wrong framework for the trials.

MF: No, the failure of the trials was for a specific reason.

DH: The patients were too mildly ill; so they weren’t able to show a distinction between drug and placebo in the trials. Were there further issues?

MF: I’m going to tell you one of the issues.

DH: Please do. This is very interesting.

MF: Dr. Raoul Desjardins, a physician, was the head of a company that monitored commercial drug trials in the United States. He ran the trial, and we picked the sites together. After some months we visited the three sites and two months later we visited the three sites again and on the second or third visit, he became suspicious of the work records. I did not understand what his suspicion was, but as we left one of the trials in Boston, he said, “I’m going to come back with a team but I don’t need you.” Sometime later he called me and said, “I’d like you to come with me, we’re doing another site visit”. We went to the site and he asked the investigator, who’s well known, to please pull any chart. He pulls one and it’s incomplete; numbers are missing, dates are missing. Then, when I saw the master sheet has one date and the chart has another date I asked, “How did this come about”? The investigator replies, “Well, he’s taking care of it, ask him”, pointing to a clerk, a young man, probably a Bachelor candidate, not a physician or a nurse. Desjardins and I went to a second site and the records were also incomplete in the same way. Both sites had been selected for competence and experience. Everybody agreed they were well known; both of them had NIMH grants. They were part of the pharmaceutical establishment. The one in Boston had too many
drugs to study. In fact, some of the charts had two drugs recorded at the same time, which is unheard of, so that study was cancelled. The Dutch were faced with the dilemma of what to do with the data? They sealed the three studies in the submitted files to FDA but without request for FDA analysis or approval, and decided that they would pursue a sister drug, ORG-3770, mirtazapine. It had the same EEG profile. I’d published the paper to show that 6-asamianserin with two isomers had equivalent EEG patterns similar to that of mianserin. The pharmacologists in Holland thought that one isomer was active and the other was inactive. We did an EEG study in humans with isomer A, with isomer B, and the combination, with the same doses of isomer A and isomer B, and the combination at equivalent doses. The EEG response was the same for all three. It was published in *Psychopharmacology* in 1982. It’s another fine study of the power of pharmaco-EEG trials. They made a business decision to wait and, a few years later, they came to America with it.

DH: With Remeron (mirtazapine)?
MF: Yes. It was after that, that all these newer agents were introduced with emphasis on this or that neurotransmitter. Mirtazapine was also more sedating than the public liked, which was true for mianserin, as well.

DH: True.
MF: Mianserin ended for various reasons, but I think sedation was one of them, was it not?
DH: There was a big fuss in Europe about it that it causing a drop in the white cell count.
MF: It’s possible.
DH: This was around the period when drugs like fluoxetine (Prozac) came on the scene. I think the marketing of the SSRI’s was much better.
MF: The director of research for Organon became a personal friend, his family and my family. He sent his daughter to America in 1976 to stay with us for a couple of months to learn English. His name was Jack Vossenaar. I asked: “Jack, with mianserin, did you get your money out of it”? “Max, I was promoted because mianserin worked”. “Promoted”? “Yes, I became the overall director of research for the whole company; before I was only in neuropharmacology, but they liked what I had done, so I became the director. You know, pharmaco-EEG worked”.

DH: Absolutely.
MF: In the real world, what counts is money.
DH: Right, but we don’t have it nowadays. How different would the field look, do you think, if we had more pharmaco-EEG now?
MF: My clinical experience with some of the new drugs is limited. I ended my clinical experience in 1997. From 1980 to 1997, I was a staff psychiatrist
at University Hospital at Stony Brook, a thirty-bed unit, and during the six months that I was on rotation I cared for the patients in fifteen beds and taught the residents. The other six months I would teach and do research. When the new drugs came in, like fluoxetine, we were not doing pharmaco-EEG studies anymore. That ended at Stony Brook in 1986, mainly because finances dried up; industry wouldn’t support it; NIMH wouldn’t support it; although, Jonathan Cole was anxious to continue it. More importantly, my interest had shifted to ECT.

DH: What was your experience with fluoxetine?
MF: My first experience with fluoxetine was with inpatients. We gave it to patients at increasing doses. It didn’t work very well. When it seemed to fail we gave the patient imipramine or ECT and the patient improved. Again the drug had limited success.

DH: What about atypical neuroleptics?
MF: At the doses that had been recommended, I saw no effect on cognition, no sedative effect and no effect on any of the physiologic measures that I experienced with other drugs. I would say today that if the pharmaco-EEG analysis of the atypical neuroleptics and the new antidepressants were to be done, they would show little difference from placebo at the doses that are recommended. Whether they might be of some benefit at higher doses is unclear. Some EEG studies of these drugs are reported but the studies are poorly done, not well controlled. The pharmaco-EEG world ended about 1990. We had developed a fine technology and methodology for dosing, quantification of the EEG that created a science. But some clinicians did not use quantitative measures; they would look at the wiggles and say, it works or it doesn’t work.

The classic story is that of clozapine (Clozaril). In the 1990s, a poster session came out on EEG with clozapine at different doses. It came from NIMH, and said at high doses the drug produced seizure activity; they recommended the limit should be set at a dose before seizure activity, monitored by blood levels. After that the efficacy of clozapine declined. Nobody benefited at the lower doses. In order for clozapine to be effective the EEG has to show the changes that an untutored EEG observer might call “abnormality”. Well, what’s an abnormality? An EEG with seizure-activity is a normal effect of clozapine at effective doses. The benefit comes from the seizure-like activity. I don’t know what the physiology of these high voltage slow waves with spikes is, but it is not “abnormal”. It is normal with clozapine. I believe that every patient successfully treated with clozapine will exhibit spikes and slow waves; it is normal for that drug.
DH: I want to quickly take you to the history of the field. The conventional histories of all the people that have been interviewed here for the last ten or fifteen years would say that the field began with chlorpromazine in 1952. They would say that chlorpromazine is the best effective agent we have to treat people who’ve got mental illness. I know you don’t think that’s the case; that it began twenty years earlier with the use of barbiturates to treat catatonia. Could you take me through the history of that, and also how you came into the area?

MF: The catatonia story?

DH: Yes.

MF: What a delightful question! When I was a resident at Bellevue, I went on the wards in psychiatry in a little white coat. It had two side pockets and pens in a breast pocket. In one pocket, I had a box containing a syringe and needles. Every night these were sterilized by autoclave. In order for the needles to be sharp, I sharpened them myself. That’s the level we were at. In my other pocket, I had two wooden tubes containing amobarbital sodium (Amytal) 500 mg each and a tourniquet. Very often, a nurse or an aide would call me to an excited patient in restraints, or one who was a posturing catatonic, or a manic. The catatonic patient was easy; put a tourniquet on and inject amobarbital. The most dramatic thing occurred; patients who were posturing, mute and not feeding would quickly respond and talk or begin eating. A few hours later they would be back in their posturing, back in their mute state. I didn’t realize it at the time but those patients were all sent for ECT. I did not work at ECT in my residency at Bellevue. So, I just didn’t see it.

DH: How was the effect of amobarbital on catatonia recognized?

MF: The story is documented in a magnificent silent film from 1930 that is available at the National Library of Medicine. William Bleckwenn described the effect of amobarbital on four catatonic patients, each posturing with arms outstretched. One patient was rigid with the legs up and head up, in a U shape position. After amobarbital he is seen talking. You see his mouth moving but the response is not heard. Bleckwenn has a line on the bottom: “The patient is catatonic” and then the box says, “2 grams amobarbital.” The next person is walking back and forth after being pictured posturing and still. Another is a woman, sitting frozen and staring, and next you see her eating, she’s hungry and she’s moving both hands to feed herself. That was the beginning of psychopharmacology in the modern era.

Four years later, Ladislas Meduna in Hungary treated his patients by inducing seizures. Psychiatrists in Hungary found Meduna’s the original records of Meduna’s experiments at the hospital called Lipótmetső.
A paper on that is going to appear this March (2009) in the *Journal of ECT*. Of Meduna’s first eleven patients, nine were catatonic: five were mute and tube fed.; four were posturing and rigid. I can only say that God was good, if there is a God, because had Meduna first selected schizophrenic patients of the paranoid or hebephrenic types he would not have obtained the positive results that he did with the few seizures that he induced. Catatonia is immediately responsive to ECT. In my work at Hillside, St. Louis and New York I paid little attention to catatonia. Like many others, when the drugs came, I assumed that catatonia had disappeared. I didn’t see it very often; my students, however, did. Richard Abrams and Michael Taylor wrote three fine papers on catatonia in manic patients in 1976 and 1977.

My interest in catatonia began in 1987 at Stony Brook. I was in charge of ECT, and one day Gregory Fricchione, a Harvard graduate, the attending in charge of the Consultation-liaison service, said he had a patient on the medical service that was catatonic and he thought I should give the patient ECT. The patient had been in the hospital for many weeks, was being tube fed, had an IV, and was in restraints periodically. She had malignant catatonia with both the manifestations of excited and stuporous catatonia. I used to give “hands-on” courses in ECT and that day I had four students. We did the consultation together. One student is now a professor of psychiatry at a medical school. The others are practitioners. We agreed that she was catatonic with a history of mania. The patient had lupus erythematosus and the lupus expressed itself in a catatonic state. I asked: “Would any of you be willing to give this patient ECT”? Three students said, no, because she’s too sick. But, the future professor of psychiatry said, “Max, you’re not going to treat this woman, you can’t, she’s going to die” and he was the most emphatic. The other three were not sure of themselves. I wrote my chart note saying: “Accept for ECT immediately, but if we’re going to give the patient ECT, we will give treatments three days in a row” and I signed my name. The medical department, the parents and husband all went into panic. A week went by. Greg Fricchione asked whether I would meet with the family. I did, and pointed to the reality that she was dying; she was losing weight and the internists had given up on her. Consent was given and we treated the patient. She recovered dramatically. She left the hospital, fully capable of walking and talking. Then I told Greg to send me any catatonic he found and I would treat them.

Over the next few months he referred other catatonic patients, then another patient in manic delirium. On the day of the second ECT, the manic calmed down and no longer needed restraints. The day of the third ECT,
he said, “I want to go home”. It was most dramatic. That got me interested in catatonia. The lupus case was published in 1990 in the *American Journal of Medicine* and after that I got in touch with Mickey Taylor. In 1991, Taylor and I published our first paper on catatonia; how to identify it and argued that it should be separated from schizophrenia in the upcoming revision of the classification. In the next decade we worked together and in 2003 we published *Catatonia: A Clinician’s Guide to Diagnosis and Treatment*, in which we covered everything that we could find in the literature and from our experience. We have since argued to make catatonia as a specific entity in DSM-V, in “a home of its own”. In 1980, a commentary in *Psychological Medicine* asked “Where Have All the Catatonics Gone”? I don’t know where they’ve gone since we still find them in about 10% of in-patient psychiatric services; they’re just not often recognized. Actually nowadays, catatonia is being recognized as a motor syndrome. We urge the use of lorazepam (Ativan) as a specific diagnostic test. If the patient responds to an intravenous dose we recommend treatment with lorazepam at high doses. Eighty percent of the patients meeting our catatonia rating scale criteria at Stony Brook responded to lorazepam. Twenty percent had to be treated with ECT, a pretty good record, I think. Incidentally, every person that we’d treated, except three, at the time we wrote the book had recovered. Three patients did not recover and each failure we view as the result of inadequate treatment.

DH: In the wider public mind, the thing you’re most interested in is ECT. Now, you’ve been part of ACNP from the start. ACNP hasn’t always been the friendliest organization for ECT. Can you link those two stories together for me?

MF: When ACNP started, about a third of the members were clinicians; physicians treating psychiatric patients and carrying out drug studies. About a third of the members were psychologists, most often interested in behavior measures; and a third were laboratory chemists and physiologists. In the first decade there was a strong emphasis on the clinical issues including an interest in EEG. We held a number of pharmaco-EEG panels. There was also some interest in ECT. At the time, we discussed the conditions for which ECT was applicable, as in patients who don’t do well with antidepressants or antipsychotics. In the early 1970s the California legislature restricted the use of ECT, and the treatment became “controversial”. Members of the ACNP, by and large, cut off interest in ECT. Since 1980, there’s been zero interest. There’s been some nascent recent interest because of the enthusiasm for brain stimulation as a new gimmick. A Brain Stimulation Symposium is scheduled for this afternoon. There was one either a year or two ago.
My active involvement with the ACNP was at the very beginning. I was a member of a number of the committees. I was chairman of a Nominating Committee the year that we nominated Nathan Kline, which, by itself, caused a furor, because Nathan Kline already had a reputation as being somebody who did multiple trials, etc. Nevertheless, he was a leading clinical figure and became President. Originally, there was some interest in the ACNP in such things as, “How Does One Make A Diagnosis”? I had two evening sessions on “catatonia” that worked out very well, because there were people in the audience who stood up and said, “You’re imagining things, you’re seeing cases we never see; they don’t exist.” More recently interest in these topics has been non-existent, not only here, but also in the New Clinical Drug Evaluation Units (NCDEU) and Biological Psychiatry meetings.

A few years ago I was appointed to the ACNP History Committee and I chaired it for a year and had a wonderful time. The function of the History Committee at that time was only to invite an annual lecturer. We had debates on who to invite. Now, they’ve taken over the Archives and that’s an interesting feature. My own archives are at the University of Stony Brook Library, rather than here.

DH: Most people from the outside see in ACNP a group interested in the physical treatments given people who are depressed or have schizophrenia. But you’re at odds with that in the sense that you’ve seen the drug treatments push ECT out of the field. Could I ask you to talk about that?

MF: ECT began in the 1930s, and at first in America and around the world, it was very actively used. For two reasons; one, most of the patients who were mentally ill were in big mental hospitals and ECT was a way of reducing the mayhem that occurred in the hospital. A wonderful paper described the reduction in the number of fires set and the number of windows broken after ECT. Then chlorpromazine came, in in the 1950s and imipramine, in the 1960’s. Studies were done in which patients were randomly assigned either to ECT or imipramine, or ECT or one of the other antidepressants, or ECT or chlorpromazine. There was even one study of ECT vs. monoamine oxidase inhibitors (MAOI). When these were published in the early 1960s, they all said essentially the same thing. The criterion for evaluation was dischargeability; the rating scales and the dischargeability criteria showed that the drugs were equivalent to ECT. Not really equivalent when you look at the data, particularly in some specific studies published from California in which the ECT was superior, but the difference was not that big. Instead of having a 40% remission rate with drugs, ECT developed 48% to 52% remission rates. The end result was to discard ECT for two reasons: one
was that ECT was not done well, doctors weren’t interested and there
was no science behind ECT. The second was that if they were almost
equivalent ECT could be put aside since pills are easier to use, less
expensive in manpower, and more easily accepted by the public and
patients. Also, the doctor did not have to leave his office. Some studies
reported better results for ECT in depression, mania, and schizophrenia
but this was a mixed bag. Some of those diagnosed as “schizophrenics”
were major depressives with psychosis; some, in retrospect,
were surely catatonic and responded very well; and some were obviously
chronic hebephrenic and paranoid, and did not respond well. So, a
dichotomy of ECT response was reported. It was also that some who
responded responded within the first six to eight treatments whereas for
others it took twenty-five or more. The attitude developed that ECT was
difficult to use and not much better than pills.

The appearance of Scientologists was another factor. Then some liberal
minded academics like Thomas Szasz and Peter Breggin, as well as
former patients, began to attack ECT. Physicians faced with the choice
of maintaining ECT as a practice and dealing with Scientology or, as in
California, with restrictive laws, opted out and no longer considered ECT
for their patients. California passed a law in 1973 that restricted the use of
ECT. Doctors went to court and the court agreed that the California legis-
lation could not restrict ECT, restrict practicing medicine. The California
legislature then passed a new law requiring detailed recording of treat-
ments, including ECT and lobotomy and that created a big limitation.
They also passed, as part of that law that anybody under eighteen had to
have an adult other than the parent give permission. So about 1975 ECT
essentially stopped in California. The American Psychiatric Association
created a Task Force, which met from 1975 to 1978, and their report in
1978 said ECT is very effective for certain conditions and defined them.
It also said ECT is a treatment that needs more research on methodology
and that we were unclear about equipment and monitoring seizures. Most
importantly, the report said that ECT required voluntary written consent.
That was the first time the American Psychiatric Association argued that
the patient must give his or her signed written consent for a psychiatric
treatment and the consent issue has become fundamental in clinical ECT.
Now, this day, a written consent for a psychiatric treatment other than ECT
is not required in most states. Basically, a physician can prescribe any
medication and forcibly give any medication if the patient is a risk to him-
self or to others. We can’t do that with ECT. And, so, by the late 1970’s
and early 1980’s, ECT effectively disappeared from America and around
the world.
DH: You are now seen as the key person in insuring that ECT did not disappear completely. How did you get pulled back into these issues?

MF: It’s a very interesting story. When I left Hillside Hospital in July 1962, I moved to St. Louis as Director of the Missouri Institute of Psychiatry. We had patients, the chronically ill, kind of patients usually seen in state hospitals. I did not open an ECT unit in the four years I was there. We did everything with psychotropic drugs. ECT in many hospitals and many research units disappeared. When I came back to New York I did not open an ECT unit until 1968, and the way that happened was partly research and partly happenstance. New York Medical College did not have an ECT suite or unit. A resident named Richard Abrams came to me. He had spent two years in the United States Army Medical Corps and wanted to do a study of unilateral vs. bilateral ECT. I went to the local Gracie Square Hospital where ECT was an active service and said I would like to do a research project and could fund it. They agreed. I wrote a grant application to NIMH and asked for funds to compare unilateral vs. bilateral ECT as well as multiple treatments in one session (MMECT) vs. single treatments in a series. I equipped an EEG laboratory, put an air conditioner in the wall, and hired a nurse from the New York Medical College who would come to the hospital, when we needed her. Most interesting was the NIMH site visit. We were asking for three years support and they requested a timeline of what I expected to do each six months. When I got to the end of the fifth six months I still hadn’t finished the data collection. One of the site visitors, Arnold Friedhoff of NYU, said he thought I needed four years support and so the grant was awarded for that. That study showed that bilateral ECT was better than unilateral ECT and that multiple monitored ECT had more risks compared to single treatments and it was not more effective. Those papers were published in, I guess from 1971 to 1973. The work was done between 1968 and 1972. I was appointed to the APA Task Force on ECT because I published those papers. The studies were well controlled, well monitored, using EEG monitoring and rating scales.

DH: At this point you had done the research but you hadn’t become firmly committed to the idea that ECT had to be saved, had you?

MF: In 1978, I was an author of the APA ECT Task Force Report, and after the report was published a number of hospitals, encouraged by the positive nature of the report, decided to start an ECT service, and invited members of the task force to give a lecture or help set up a service. I had a manual on how to do that. At that point I also became interested in the mechanism of ECT and in 1979 I took a sabbatical from Stony Brook to write a book on ECT. There’s an odd personal issue there. The Task Force had five full members and two advisory members, so there were
seven votes on any recommendation. On a number of issues, the words in the manual were written after a vote of four to three. I said if we weren’t sure of the answer we should leave it open, inviting research clarification. But the Task Force wanted to give guidance to the field. So, those four to three votes gave me heartache. At the end, I was almost ready not to sign the document. Then, I decided to write my own book and, in 1979, I wrote *Convulsive Therapy, Theory and Practice* that was published by Raven Press in New York. I took every issue that had been arbitrarily decided by the Task Force and explained the pluses and minuses of what was known. That book is, I think, the best I’ve written on ECT, even compared to the new one. So that was how I got interested in reviving ECT.

Another push came when NIMH organized a meeting of ECT researchers in 1978. There had been an earlier meeting in 1972 the proceeding of which was published as the *Psychobiology of Convulsive Therapy*. The meeting was organized by NIMH and held in Puerto Rico. It took awhile to get the papers published by V.H. Winston and Sons, in Washington DC, in 1974. That book described the neurophysiology, biochemistry and neuropsychology theories at the time. Those were the three elements discussed with not a word about endocrinology.

By 1977, the APA ECT Task Force had presented some of its conclusions, and the NIMH agreed to the second investigators’ meeting in New Orleans in May of 1978. At that meeting the issues were different. Mechanism was the focus, and one session was devoted to “Could Endocrines be an Issue.” Jan-Otto Ottosson presented his ideas and a very similar experience occurred to what had happened with Itil and me in 1958. Independently, we had read the literature and had come to the conclusion that the peptides in the hypothalamus must be a factor in the recovery process after ECT. The evidence we used were the DST and TSH response data with some other neuroendocrine material. We published our neuroendocrine theory in 1980. Next, I applied for and got money to do further research on ECT. We were interested in how to monitor effective seizures and the outcome of treatment. Many of the studies at that time lacked EEG monitoring, so when the doctor said the patient had eight treatments and yet did not get well, we did not know whether the seizures had been adequate. We were able to argue that you have to record, a seizure duration of at least 25 seconds or longer and show EEG seizure activity of slow waves and spikes, and to have a sharp end point as markers of an effective treatment. It took a while to develop those criteria. Looking back, many of the studies of the 1980s and 1990s were done poorly. To this day, there are reports published in which a depressed patient has failed drugs and ECT but when I look at what this meant, in
many instances it was not the ECT that failed, but it was the clinician who had failed by failing to develop adequate seizures. It was the same as prescribing pills without ensuring the patient takes them.

DH: A lot of people would say you’re the person who did most to save ECT in the US and maybe, worldwide. Is that the thing you wish to be remembered for, or is it the catatonia or the pharmaco-EEG story? Or should all of these that you should be remembered for?

MF: That’s a wonderful question. I have recently taken my archives, which are all my records from 1950 to a year ago, and deposited them at the University Library at Stony Brook. As part of that process I opened some of the boxes. At first I was going to censor the material and then, I thought, this is nonsense. It’s not for me to decide. The world will decide twenty years or thirty years from now whether pharmaco-EEG was an error in science or an important step in learning. They surely will learn about ECT. They might learn about my work with opioids and opioid antagonists. The issue about my life is that I was a researcher, who learned early the importance of control studies, random assignment, monitoring, and independent evaluations. I learned all the things which make up a wonderful study; that’s what I tried to do. If you ask what the best papers are, is that reasonable?

DH: It is.

MF: My paper on chlorpromazine and insulin coma I consider very important. It had a profound effect on my career, because the hospital then gave me a lot of money and whatever I asked they were glad to give it to me. Then, NIMH gave me money and I expanded my research quickly. By 1958 we closed the insulin coma unit. Other important studies were monitoring the ECT and the 1972 conference on theory. In 1958 I had written a theory of ECT based on neurophysiology. It’s called The Neurophysiologic Adaptive Hypothesis. I applied to NIMH many years later to test the theory. Richard Abrams, Jan Volavka, Rhea Dornbush and some others worked on the project; that was done at Gracie Square Hospital. We concluded that the neurophysiology measures were an index of immediate response but were not related to therapeutic outcome, that the neurophysiologic theory was wrong. In retrospect, the study failed to support the theory because we didn’t have proper diagnoses for the patients. If we had tested the theory in relation to catatonia or melancholia it would have worked, but in those days patients referred for ECT had a variety of diagnoses. We confirmed that ECT requires seizures and that the mechanism is not in the neurophysiology changes we measured but was inherent in the seizure.

The second ECT mechanism I hypothesized was the “cholinergic hypothesis”. That was published in 1966, and was not supported. The
third hypothesis was published in 1980 with Ottosson and that’s the “neuroendocrine hypothesis”. I would like to think that the “neuroendocrine hypothesis” at the present time is still the best explanation of ECT.

I did some of the first experiments with naloxone in opioid dependence, at the same time as the people in Lexington and, following our work, it became obvious that everybody should have Narcan freely available in emergency units, so that they could give naloxone to patients admitted to the hospital in stupor or coma. The first time this happened I received a call from a hospital in New York City. I was at home in Great Neck, Long Island and drove into the city; they had a man in stupor secondary to opiate overdose. I gave him naloxone IV and he woke up. It was a very dramatic experience, the fact that naloxone actually wakes up an opioid dependent subject. But then I made a fundamental error; naloxone was short acting and I did not take that into account. Opioids are long acting and the patient went into stupor again after I had left. I got another call. I told the resident to get another batch of naloxone and to inject it again, as often as necessary. In the morning we had given him naloxone every 2 to 3 hours until the opioids were gone, the best demonstration of naloxone’s efficacy.

With pharmaco-EEG we developed a quantitative science, showing that the quantitative EEG was a worthwhile measure of drug effect using digital computer methodology. I’m sad there was commercialization of the pharmaco-EEG model. I heard that in California some doctors are promoting pharmaco-EEG as a predictor of drug effect in the individual and of clinical diagnosis. That’s nonsense; it does not work. What the pharmaco-EEG record can tell you is whether a drug is active or not; it does not give a diagnosis.

Then, I got interested in catatonia and suddenly realized that catatonia is not schizophrenia. Working with Mickey Taylor, we published a book about that and I’m working very hard to convince the DSM-V Task Force to put catatonia in a category by itself; “in a home of its own.”

After Taylor and I finished our catatonia study and our book was published, we met in Chicago. We discussed our finding that catatonia is remarkably responsive to benzodiazepines and to ECT. We had only three treatment failures, but many, many successes. When you take the catatonia rating scale and give lorazepam to a patient, if the symptoms resolve, even temporarily, by a fifty percent reduction in the scale that is, a verification of the diagnosis of catatonia. The validation is when you give the patient high doses of lorazepam or ECT. In our study at Stony Brook, we had thirty plus patients that followed this protocol. Everybody labeled as “catatonia” was given a lorazepam test. The 82% who had
a positive response to the single dose of lorazepam had a positive response to lorazepam treatment at high doses. But 18% did not respond to lorazepam. We gave them ECT and they all resolved. So, catatonia is a definable entity. It is a biological syndrome. It should be a separate entity in the DSM and I hope I’m alive to see it.

If the commissioners don’t include it as a separate entity, then it’s a repetition of the earlier errors in DSM-I to IV, which is purely descriptive and not based on biological etiology.

My next contribution is in melancholia. After publishing Catatonia, Taylor and I were celebrating at brunch in Chicago and asked what are we going to do next? Taylor said, “There is one other condition that responds to ECT and that’s melancholia”. But what is melancholia, and how do you define it? We worked for three years and wrote Melancholia: A Clinician’s Guide to Diagnosis, Pathophysiology and Treatment of Depressive Disorders, which was published in 2006 by Cambridge University Press. We argue that “melancholia is a syndrome”, a mood and motor syndrome, which is defined by specific characteristics. They are depressed people with vegetative and motor signs; they have symptoms in all three areas. When these patients are examined for cortisol function, a large percentage, we don’t have a definite number have elevated serum cortisol and failure to respond to the steroids that suppress cortisol. When a melancholia patient with all three characteristics plus cortisol abnormality, is treated with a tricyclic antidepressant (TCA) in adequate dosage there is an 80% response rate. That’s what the old literature shows. We don’t have a new drug study to prove it, but with ECT there is a 90% resolution of melancholia within three weeks. And if the cortisol abnormality does not resolve, that’s a sign the patient needs more treatment. So, cortisol abnormality is an index of severity of illness and of the presence of this type of depression.

DH: All the people interviewed say that the ACNP helped them hugely. In your case, in terms of ECT and melancholia, catatonia and pharmaco-EEG, how has the ACNP helped, or have you been at odds with the organization?

MF: In the first decade, Itil and I and others submitted symposia, clinically related, about pharmaco-EEG and they were accepted on the program. We ran two or three hour sessions before there were posters. We also offered ECT sessions and they were accepted. So, every other year we would have an ECT session or a pharmaco-EEG session. I said that badly; Pharmaco-EEG was active before ECT. ECT came in the 1980’s, and we had a number of symposia at that time, not well attended, but they were here. Once we learned the mechanism of ECT with the neuroendocrine
hypothesis we had one symposium in the late 1980’s, and that was it. Then, whenever we submitted symposia, they were rejected. A symposium was suggested for this meeting. Dr. Lisanby of Columbia University was the senior author and it was rejected again. I have always considered the ACNP as not very supportive of anything that I did regardless whether it was insulin, ECT, pharmaco-EEG, or psychiatric diagnosis. I’ve been outside the mainstream of the society, especially when it became enamored with laboratory neuroscience. Rather than a College of psychopharmacology, once they turned to neuroscience, clinical issues disappeared. About ten or twelve years ago, Donald Klein got very upset with this society. He and I submitted clinically related symposia but they were rejected. Klein then organized the American Society of Clinical Pharmacology, ASCP. I was an original member and that society still exists. For a while, it had funding from private sources, but now they are also dependent on industry funding. They do not have a meeting with individually submitted presentations. They run annual teaching sessions that give attendees a test after the sessions and award certificates of attendance in psychopharmacology. They invited me once or twice to teach a session, but they, too, are not interested in ECT, in the EEG or in clinical syndromes other than bipolar disorder and anticonvulsants, depression and SSRIs, and schizophrenia and atypical antipsychotics; subjects of interest to the pharmaceutical industry. If you were to ask Don Klein at this point, I think he would say that the ACNP has become too neuroscience-oriented, that the clinicians; physicians, psychologists and sociologists have all disappeared and the symposia now are mainly related to industry projects and proposals, or to fantasy neuroscience.

DH: A big concern at this meeting has been the issue of links to industry, how people who’ve been senior figures in the field have ended up on the front pages of The New York Times. How do these issues look to you, the links between ACNP and industry, and where do you think the future lies?

MF: I knew of the control by industry in the late 1980’s when they took over the American Psychiatric Association. Parallel to my experience with ACNP, I submitted symposia to the APA and they usually turned me down. They would accept a symposium on ECT or NMS every once in awhile. It would be presented Thursday afternoons, the last session, the last afternoon, and I’m sensitive to that. The APA had a task force in on ECT in 1978 and another that met and produced a book in 1990. We had a symposium the next year and the year after, but following that they turned down our submitted symposia and I got upset. I believe that the APA has been fully taken over by industry. They say they’re trying to change that, but I have my doubts because the APA is so beholden to industry to
support their exhibits and the thousands of people that they bring from overseas. The ACNP has made an attempt, I understand, to deal with this issue but the leaders of the society are intimately tied to industry.

This morning I walked into a paper session here. A member of this society Michael Thase put up a slide showing his association with industry for conflict of interest and the audience roared, there was big laughter. He offered the list of his consultancies and research grants, there must be forty, maybe fifty on the list. And what did he say when showing the list; “Because I work for every company, nobody influences me!”, and the audience roared again. That defense is silly. Leaders of this organization are intimately tied to industry and they do not provide data that would permit a reasonable clinician to evaluate the benefits and risks of the new drugs, in order to prescribe optimally. I have said, publicly, that I have stopped using any drug produced after 1980. None have been tested independently and with time their inefficacy and risks are better understood. I will not recommend any drug unless it was tested before 1980. That’s not altogether true. There are some new drugs in medicine that are fantastic, like etanercept (Embrel) for psoriasis, but in psychopharmacology I know of no new drug that has been effectively tested and for which we know the positive and negative aspects with confidence. The data are very strongly compromised and I am sorry that this society has not taken a stronger position. They say they’re doing it and I hope so but the fact that three former presidents have gained notoriety in the newspapers, and a few others probably will, makes me very nervous. I also am concerned that the DSM-III and DSM-IV have been very poor models for diagnosis and treatment and I am trying very hard to get DSM-V to consider catatonia and melancholia as separate entities. For catatonia we can make the diagnosis based on behavior, verify it by laboratory tests, validate by treatment with an outcome of ninety percent or better. The same is true for melancholia. That’s what I think should be done. But as I’ve talked to people today and I met with skepticism. I am tilting at windmills and I suppose that’s a good way to end this interview. I’ve been a Don Quixote figure for a long time.

DH: Okay.

MF: Thank you very much.
TB: This will be an interview with Dr. Louis Gottschalk for the archives of the American College of Neuropsychopharmacology. It is April 6, 1999. We are in Nashville Tennessee. I’m Thomas Ban. Please tell us when and where you were born and something about your education and early interests.

LG: I was born in St. Louis on August 26, 1916, the third of four sons. My father was born in the United States; of German heritage and my mother was of French-Swiss background also born in the United States. I’m a typical mixed ethnic background American. I grew up in St. Louis where my parents and maternal grandmother taught us to speak French at home. My father was a very gifted man with a law degree who never practiced. As a child he was taught to be a good musician and artist who wrote for the St. Louis Post Dispatch as an art and music critic. He was a gifted violinist and pianist, who composed for quartets, quintets and even opera. The joy of being creative influenced my childhood and development. On my mother’s side my Uncle Louis went to Paris to study art and became an architect and builder; so both sides of the family were artistic and musical although I wasn’t very good at those things. Still, my parent’s easygoing efforts encouraged us to write or be creative and that behavior was imprinted.

TB: Could you tell us something about your education?

LG: I was growing up in the depression years, 1928-1934, and my older brothers got to go to college, but, by the time I came along, the family didn’t have any money so I went to a public vocational school, learning secretarial skills and accounting. When I did finally go to college, I had a lust for knowledge. I felt deprived and eager to learn. I went to night school at Washington University but didn’t know what I wanted to do. I was interested in everything that came along, whether it was English or Science.

TB: What did you major in?

LG: I had a major in Biology, Psychology and English.

TB: A triple major. Was there anyone else in the family with an interest in science?

LG: My father had an interest in science and his younger brother, Victor, had a PhD from the University of Chicago in Physics. So, the family was interested in both Arts and Sciences. It probably brushed off on me.

TB: Obviously, it did. After college, did you go straight to medical school?
LG: Yes.
TB: So you did not have any delay between college and university?
LG: No but I was delayed from high school going to college, because of financial reasons. There was a two and a half to three year lag. In that period I was a clerk in the First National Bank of St. Louis and did a lot of other things. It was good for me; I was more mature and really motivated to go to college.
TB: Where did you study medicine?
LG: At Washington University in St. Louis.
TB: An exceptionally good school.
LG: I didn’t realize how good it was, but I was certainly inspired in medical school. As an undergraduate at Washington U, I had some outstanding professors, like Frank Webster and Dana Jensen in English, Victor Hamburger, in Experimental Embryology who probably should have won a Nobel Prize. I also had Holly Compton, a Nobel Prize winner in Physics. There were seven Nobel Prize winners at Washington University Medical School, they were inspired and it brushed off on us.
TB: Could you give us the names of the other two and also for what did Holly Compton got the Nobel Prize for?
LG: He was a physicist. I can’t say why he got his prize. At medical school, there were the biochemists Carl and Gerty Cori; and there was a physiologist, James Erlanger. They were not only fine researchers but very enthusiastic.
TB: When did you decide to enter psychiatry?
LG: The only reason I went to medical school was to be a neuropsychiatrist.
TB: I see.
LG: I don’t know exactly how it happened but I was interested in the mind and brain and why people behave the way they do, to learn about why they think the way they do.
TB: You had contact with many exceptional people. Did any of them have a special impact on your development?
LG: I should flash back to my undergraduate years. There were some great professors, like Victor Hamburger, who taught biology and experimental embryology, John Paul Nafe, who taught physiological psychology, and a woman geneticist, whose name I can’t recall. But my contemporaries, my classmates were important, also. I was surrounded by a group of unusually gifted people although I didn’t realize it at the time. There were people in my class such as Tennessee Williams, William Inge, another playwright, Josephine Johnson, a Pulitzer Prize winner, Ed Meade, who wrote *How to Succeed in Business Without Trying*, and his younger brother, Walter
Mead. They were mostly English majors. I wrote for the college magazine and I enjoyed the fun of writing or “creating”.

TB: Did you have any contact with Tennessee Williams?

LG: As an undergraduate only.

After college I wouldn’t have had the means to go to medical school, but I got a break. I met the acting head of the Department of Neuropsychiatry, Dr. David Rioch, an extremely gifted neuroanatomist and neurologist, who wrote the section in Gray's Anatomy on the extrapyramidal system. He got me a job at Washington U in the Department of Neuropsychiatry; it was a combination of neurology and psychiatry and I also had a Josiah Macy Foundation Fellowship that paid seventy-five dollars a month. That made it possible to go to medical school but I was probably the only one in the class with an outside job. I can visualize all those people I worked with. There was David Rioch, who was doing research. I was assigned to Felix Deutsch, MD., a famous doctor. His wife, Anna Deutsch, was a famous psychoanalyst who wrote on the psychology of women. There was John Whitehorn, who became chair of the department. He was a psychiatrist who had done biochemistry and developed a test for chlorides. There was another person from Yale University, Dr. Edwin Gildea, who had a degree in biochemistry as well as psychiatry, who later became chairman. Then it was George Bishop, a physiologist, who set a rare example. He was interested in nerves and skin and tested his own hand and arms for all the points where you feel temperature, touch or pain and then dissected each area. He was credited for discovering and describing the peculiar little receptors and organs for those sensations in the skin. I had a couple of assistant professors from Harvard, George Saslow, who later became chairman of psychiatry at Oregon State University, and Daniel Badal who later became professor at the University of Cleveland. Those young men competed with one another for the opportunity and time to teach us, just a few psychiatric residents.

TB: It had to be very stimulating.

LG: Very stimulating!

TB: I assume you went from medical school straight into psychiatry?

LG: You had to have a year of internship; because I was an honor student, Phi Beta Kappa and Alpha Omega Alpha, I was offered an internship in surgery or medicine. I took the internship in straight medicine. It was competitive. The Chairman of Medicine, Dr. Barry Wood, a very good professor, later became famous. After I took straight medicine, I was invited to stay on as a resident but I was still hooked on neuropsychiatry and turned it down although the offer was a great honor.
TB: So, after an internship in medicine you went into psychiatry. Weren’t you the Chief Resident at a certain point?

LG: I became Chief Resident.

TB: After you completed training in neuropsychiatry you started in psychoanalysis, didn’t you?

LG: I really started in psychiatry and neurology; and it was only later that I got into psychoanalysis. I went to medical school from December 1940 to 1943; they speeded up the time required for medical school and residency training during World War II. We had no summer vacations and the last year we were drafted into the military, but were deferred so that we could finish medical school and then serve. I completed internship in medicine and neuropsychiatry residency and then, as soon as they could, they put us to work in our specialty. They were lots of neuropsychiatric casualties and in 1946 I was at the United States Public Health Service Hospital in Fort Worth, Texas, a 2000-bed hospital on ten thousand acres. It had been a narcotic hospital, turned over to the Navy and Marine Corp, Coast Guard and Merchant Seaman for neuropsychiatric casualties. I was there for two years. We each had huge patient loads of about a 120 patients, about 30 new patients a month. Around that time, the federal government and the Public Health Service were planning the Institutes of Medicine and the National Institute of Mental Health. Because I was a hard working public health service officer the administrators in Texas and Washington DC thought, I might be a good recruit as a psychiatrist at the National Institute of Mental Health. When the buildings weren’t ready in Washington DC, they said I could have another two or three years of training, anywhere I wanted. At that time, I had neurosurgical training in mind, probably because of the example of one of my younger mentors, Dr. Daniel Badal, who did that before he switched over to neuropsychiatry at Harvard. At the same time, of one of my older mentors, Ed Gildea, said it wouldn’t be a bad idea to get some psychoanalytic training. When I applied to the Chairman of Neurosurgery for a neurosurgical residency at the Illinois Neuropsychiatric Institute in Chicago, I told him that I would like to enter psychoanalysis as well. He was doubtful whether neurosurgery and psychoanalysis were compatible and turned me down, even after I pointed out that the Public Health Service would pay for the training. So I went to see Roy Grinker, a famous neurologist and psychiatrist, and he offered me training in child psychiatry. That’s how I got into child psychiatry. I did psychoanalytic training, beginning around 1948, in adult and child analysis, at the Chicago Psychoanalytic Institute. In that setting, being interested in the brain and the mind at the same time, were not incompatible. Grinker was a famous neurologist who had
his psychoanalysis with Sigmund Freud. The University of Illinois and University of Chicago both gave doctorates in Neurophysiology and for some reason didn’t see any incompatibility between psychoanalysis and neurophysiology. People were involved in both so I was exposed to that.

TB: Before moving any further, it seems we skipped some of the research you did in the mid-1940s. Am I correct that sometime early in your professional career you did some research in psychophysiology and published at least one paper? When was that and what did you publish on?

LG: It was published in 1946, in *Psychosomatic Medicine* and it was on producing conditioned vasomotor responses in human subjects using photoelectric plethysmography. It was done at Washington U. One of my professors, Carlyle Jacobson, a physiological psychologist, got me to read all I could about Pavlovian conditioning and behavior, so that’s how I got into the project. But it was also carried out under the influence of Felix Deutsch. I was his research assistant and he had a photoelectric plethysmograph, a device that measured blood flow in the finger. I got the idea, on my own, to see whether the peripheral vascular system could be conditioned, that is whether I could produce vasoconstriction in the fingers in response to a faradic stimulus. I was also interested to see whether there was any difference between people who condition rapidly and those who don’t.

TB: What was your unconditional stimulus and what was your conditional stimulus?

LG: A faradic stimulus was the unconditional stimulus and a light on the ceiling the conditional stimulus.

TB: So, you conditioned vasomotor constriction to light?

LG: Right. I found that among ten individuals, some conditioned very rapidly after one or two reinforcements and some subjects were very hard to condition. I think it probably shows that there are some of us with a genetic propensity to have conditioned vascular responses.

TB: So, you found that people differ in their propensity to acquire a conditioned vasomotor reflex.

LG: I also had a questionnaire to study the feelings of people associated with the vascular response. The subjects who had more variability in their emotional responses were more easily conditioned. I did figure that my findings indicated that some of us have a higher vulnerability to vascular disturbances than others.

TB: What was the hypothesis you tested?

LG: The hypotheses were; can vasomotor conditioning be achieved in human subjects and are there any differences between individuals who condition rapidly and those who don’t. When I was reading Pavlov I saw that
some dogs got easily conditioned to salivary response and some didn’t. I wondered whether that happened in humans as well.

TB: Did you link conditioning to temperamental types, as he did?
LG: No, I used a two-tailed test to see whether there was any statistically significant difference. If I found any I knew there were differences between the two groups in temperament.

TB: I suppose you did everything yourself in that study.
LG: Yes. I had to do it all myself while I was working as a house officer and attending medical school. I was in a cordial environment and the department of psychiatry fostered my doing that research.

TB: What year did you actually join NIMH?
LG: In 1951, I was the first research psychiatrist at NIMH.

TB: With whom did you work and whom did you recruit?
LG: I wasn’t into recruiting; but I can tell you who was there.

TB: Who was there?
LG: The Institute was run by a doctor who had been, for a short time, at the United States Public Health Hospital in Texas. His name was Dr. Robert Felix.

TB: The first director of NIMH?
LG: He was the first director and I was the first research psychiatrist. There was a neurophysiologist, Wade Marshall, PhD, who learned that when I was in Chicago, I had done studies with epileptic children, and he thought he could collaborate with me. He wondered whether I wanted to irritate the animals in order to have seizures, while he placed aluminum gel on their brains to make them more susceptible. I declined, knowing I was free to do whatever research I might want.

TB: Whatever research you wanted to do?
LG: Yes. It still works that way, I think.

TB: Am I correct that you were involved in EEG research in those days?
LG: While I was at the United States Public Health Service Hospital, they wanted somebody to run the EEG and laboratory in the department. They let me go back to Washington U for a couple of months to learn more about electroencephalography. I already knew some, but I focused on it for a couple of months with James O’Leary and George Bishop. That was a relatively new procedure back in those days. Then, when I transferred to Michael Reese Hospital, I got involved with their EEGs; reviewing them. It was there that I asked the Clinical Services for Children to see some of the kids in whom anticonvulsant medication didn’t control their seizures. I saw a number of these children and decided to treat a selected few with psychotherapy and/or play therapy. One of my first control cases in child analysis was a five year old Polish Catholic boy, who had seizures
not inhibited by anticonvulsant medication of any kind. It was then I got the idea to see if analysis had any favorable effect. That's how I happened to get into research into the psychological trigger mechanisms of epilepsy. I think I wrote that up somewhere. That little boy did get better; his seizures stopped. I saw him about four times a week and did very classical psychoanalysis. I followed that case for many years. There's another child I saw, an eight year old boy, in whom looking through a window screen could bring on a seizure. I wrote his case up and published it in the *Psychoanalytic Study of the Child*. From that experience I got the idea of looking for the trigger process of seizures in kids, and won the Hofheimer Prize for Research in Psychiatry.

**TB:** What year did you get the Hofheimer Prize?

**LG:** This was probably in 1955.

**TB:** So you got the Hofheimer in the mid-1950s, and started your work in children whose seizures were not controlled with anticonvulsants before you moved to NIMH. What did you do at NIMH?

**LG:** When I arrived at NIMH I asked myself what I am I going to do. I decided that I would try to continue working with epileptics, and it happened that Dr. David Rioch, who had been one of my mentors at Washington U, was now head of neuropsychiatry at Walter Reed Army Hospital. I decided I should look him up to tell him what I wanted to do. He made it possible to study inpatients with recurring abnormal EEG paroxysms and EEG waves, who might or might not have visible seizures, and to interview them. This was an attempt to combine free association with neurophysiologic findings and I did that for some time. I did find the right kind of patients and I still have records of them. It was easy to identify the abnormal EEG paroxysms, they were very clear-cut. The other side of the research, listening and recording what they said, wasn’t very objective.

**TB:** What was the pharmacological treatment of epilepsy in those years?

**LG:** There were a variety of anticonvulsant medications, including phenytoin (Dilantin) and the barbiturates.

**TB:** How long did you stay at NIMH?

**LG:** From 1952 to 1953.

**TB:** Where did you go from NIMH?

**LG:** To Cincinnati. I had two children and was married to a very gifted and beautiful doctor, Helen Reller. She was a dermatologist; we were very happy and wanted more children. But even though we were both well trained and had American Boards in our medical specialties, I had a relatively small income. When I asked my superiors whether it would be possible for me to do private practice to supplement my USPHS salary they wouldn’t let me. I was offered a position at the University of Cincinnati; at
that time the University and Cincinnati General Hospital was one of the
top places for psychosomatic research. They had some famous people there.

TB: So, you moved to Cincinnati in 1953. Who was the Chairman of the
Department of Psychiatry?

LG: Maurice Levine. There were other people of scientific note; Arthur Mirsky
for one.

TB: Wasn’t Paul Ornstein there as well?

LG: He was just a psychiatric resident when I first went there and not that
famous yet. But, Arthur Mirsky was there, and George Engel. It was
a congenial place for psychosomatic research. I was into that. Later
on I became Paul Orenstein’s training analyst and knew his wife, Anna
Ornstein, who had been in a Nazi prison camp.

TB: Douglas Goldman was also there and was involved with psychopharma-
cology. Did you know him?

LG: Very well, sure. But he wasn’t on the faculty in the Department of
Psychiatry. He was in the forefront of drugs, using them a great deal, but
not in a discriminating way. He didn’t use placebo controls in his studies;
he was an enthusiast who didn’t do hard experimental work.

TB: Yet, as you said, he was very much involved in pharmacotherapy with
psychotropic drugs. He was a great clinician and had a large practice. He
was in the forefront with chlorpromazine and some of the first psycho-
tropic drugs. That was not as popular that time.

LG: Arthur Mirsky was a biochemist, interested in psychoanalysis; he made
some interesting contributions and went to the Chicago Institute of
Psychoanalysis.

TB: It seems there were many interesting people in Cincinnati to collaborate
with?

LG: Yes. George Engel was another. He was an internist who also got inter-
ested in psychoanalysis. He had an identical twin who he outlived.

TB: What was your position in Cincinnati?

LG: At first research associate professor, and later, research professor.

TB: It is from Cincinnati that you moved to Irvine?

LG: Yes.

TB: Where did you start your research on content analysis of speech?

LG: At NIMH where I had the luxury of doing any research that I wanted. It
was a researcher’s dream and I decided we needed to objectify the diag-
nosis of mental states or psychological feelings from language. Having
looked at free-associations and abnormal EEG paroxysms I got the idea
I should try to use language and see whether I could objectify the mental
state from that. I started out with a younger colleague, Gove Hambidge,
taking movies of people. We tried to put everything together; movement, tone of voice, what they said and the semantics. I realized this was more than was needed. But our work was published; we did a couple of papers together.

TB: Did I understand the name of the young colleague you collaborated with was Gove Hambidge?

LG: Gove Hambidge had also been at the United States Public Health Service hospital in Fort Worth, Texas, and was also given the opportunity to go to NIMH. He had been a graduate of Yale Medical School, and, while at NIMH they let him have psychoanalysis in New York City. After I started at NIMH, he joined me six months later. I stuck to working on the content analysis of verbal behavior but he left and never did go back to it.

TB: Then, you continued your research in content analysis in Cincinnati?

LG: Yes, having been at NIMH I knew that applying for research money is not easy. But, I applied for various research grants and got some. Among them was a grant on content analysis of language. Later, in about five or six years, when I was getting some prominence in research, I obtained a Research Career Award. It wasn’t a lot of money, but it allowed making a living with four kids and doing some research.

TB: So, you got into your research on content analysis of language because you felt there was a need to objectify mental status. Why did you choose content analysis to achieve that objective?

LG: I like to write. I like to listen to language. I was interested how do psychiatrists learn anything about anybody? They do what you’re doing now, asking questions, listening and trying to make something of the language. I had some interest in language including foreign languages. I spoke a bit of French and I studied German; languages interested me. I was also interested in the way skillful people arrive at conclusions about how somebody else feels. In Chicago, they often argued about that. I had a mentor in Chicago, Franz Alexander, a fellow Hungarian, a countryman of yours. He and other people used to argue about what a person was communicating and I wondered why do they have to argue? I found out later they just liked to argue, even when they agreed. In any case I think that got me into language analysis and I stuck to it. When you’re trying to make an assessment of somebody’s feelings, or a diagnosis, you can use a psychiatric interview, an adjective checklist, a Beck Depression Inventory, or some other assessment instrument. I was wondering whether one could have something more scientific, since people differ a lot in how they respond to adjective checklists. The reliability of checklists is pretty poor. That pushed me on to see whether I could improve on the measurement problem. I had no idea that it would go as
far as it did. I think it was a wise choice I made twenty-five years ago; we proved we could do content analysis of language, made headway in reliability and validity and computerize the methodology. That was a lucky thing, or maybe not just lucky; it took so damn much time to try to figure out how to score the scales, according to the *Gottschalk-Glaser Method*, that it was like having to go back to school. I thought, if it can be done by a human, it should be possible to do it by machine. So I stuck to that. The first grant I applied for this, from NIMH in 1975, was turned down. The pink sheet said it’s impossible to do this by machine.

TB: But you succeeded in quantifying content analysis of language and computerizing it.

LG: The same interest in getting numbers was involved when I went into pharmacokinetics and determination of drug blood levels.

TB: You were interested in quantifying whatever you studied?

LG: Exactly. Blood levels, content analysis of language, brain waves; you can measure and quantify them all.

TB: You were also interested in drug and personality interactions. You had a paper way back with a title, *An exploration of testing drugs that effect mental activity*.

LG: That paper was published in *JAMA*, in 1956.

TB: What was the drug you were using?

LG: It was pipradrol. Do you know it? Very few people are familiar with it any longer.

TB: Yes, I worked with it in psychogeriatrics.

LG: I tried to measure the reaction of people to small doses of the drug versus placebo. I got a group of pharmacologists and psychoanalysts involved. The interesting finding was how personality affected experience of the drug. People who were uncomfortable being pushed to do something, instead of getting a pleasant feeling, got anxious, whereas people who were depressed or liked to feel pushed felt better. The range of reactions to small doses of pipradrol was large and depended on the personality of the subject.

TB: Was that your first paper in psychopharmacology?

LG: Except for the paper I published on those kids in Chicago, whose seizures were not controlled by anticonvulsants. In that study I was motivated to find out whether they had incorrigible seizures or there was something else triggering them. With pipradrol I studied personality and drug interaction.

TB: In the pipradrol study did you use any test to measure personality?

LG: No, I simply asked the subjects what their emotional reaction was.

TB: So, there was no special testing procedure?
LG: The questions I asked are documented precisely in the article. At the time I did that study I was already developing the content analysis methodology. I tried two approaches in Content Analysis.

TB: Two approaches?

LG: One approach was just looking at words whereas the other was looking at words with their meaning as they were communicated in a whole grammatical clause. Using the first approach counts only the number of representative adjectives or verbs and so on. I published some rather interesting papers using that approach. In one study on suicide notes I demonstrated that you could distinguish real from false suicide notes. That was a study organized by two suicide researchers. We published our findings with the title *Are there any differences in false and genuine suicide notes*, in *Medical Psychology*. There was a difference in the use of words. I wondered whether I should stick with that approach or look at the grammatical clause, the smallest unit of verbal communication. I later decided to focus on the grammatical clause because with semantic units the smallest is a grammatical clause. If somebody says “damn” it means usually “damn you”, but taking words out of context can be unreliable and does not provide objective and valid findings. There was a group at Harvard that used just words. But the meaning of words depends on how they’re placed in a sentence. For example, there’s a “damn you” or “damn myself”. Just counting the words does not tell who is angry with whom. So I stuck to the grammatical clause.

TB: Speech and content analysis is central to your research, and one of your important contributions that historians will be interested in. Could you describe for me what you were using to arrive at a reliable and valid assessment?

LG: I’ll give it a shot. This remains a problem although I’ve been publishing in the area for 25 years. The whole process has grown, so it’s got more and more complicated and when I try to explain the procedure, and how you can teach a dumb computer to do it, it is rather difficult.

If someone is interested in the details they should go to the original writings. But let me give it a shot. How can one measure the magnitude of anxiety, the severity of schizophrenia or cognitive impairment from five-minute speech samples? One problem is how can you standardize what somebody says? This was the first step and to do so we borrowed some ideas from psychology, namely from projective testing, specifically from the Thematic Apperception Test. We developed a standardized way of eliciting speech and these were the instructions; “This is a microphone to study speaking and conversational habits. I would like you to talk for five minutes about any interesting or dramatic personal life
experiences you’ve had. While you’re talking, I would prefer not to reply to any questions you might have until the five minutes is over. You can talk about one experience and if the five minutes is not over, you can talk about another. Do you have any questions now”? The subject might ask, “What is interesting or dramatic”? The answer was: “I don’t know what’s interesting and dramatic as far as you’re concerned, don’t worry about me, just whatever you think”, purposefully turning the question back to the speaker. “Do you have any questions now?” If the subject said they did not, then the interviewer said, “All right you can start now and, then, in five minutes, I will tell you to stop”. To get a reliable sample, a person had to speak at least 85 words. Less than that in a five-minute period, the sample wasn’t good enough. It’s just like getting a blood sample; if the sample is too small the results may not be reliable. The speech samples were recorded and the transcript typed in text, ASCII or word perfect 5.1 and lately in Microsoft Word, because the artificial intelligence software program, LISP, is programmed to understand these computer programs. The speech sample was scored after it was typed up and punctuated with the insertion of periods and commas. The program needed help in case of a compound sentence that had to be separated by a comma. So the typist put in a slash or diagonal to tell that a clause had occurred. Now our software program recognizes and does all this clausing by itself. The key question is what do you examine in the sample? It qualifies the word and examines its meaning. The program is doing that by understanding all “parsing.” Parsing is a capacity to label each part of speech, as noun, pronoun, adjective, verb, adverb, preposition, conjunction, and so on. All that information, over 200,000 words, has been put in the memory of the computer to teach it the words and their meaning. It knows that a word like “hide” can be a verb or it a noun. It also knows there’s a difference between, “He hit me” and “I hit myself”. It makes a difference in psychiatry whether you’re going to conclude, “I like myself” or “I hate myself” or “Somebody doesn’t like me”. In addition to having the semantic knowledge of over 200,000 words or idiomatic phrases, the computer knows every slang expression. If somebody says, “I’ll kick the bucket”, it knows that doesn’t mean somebody literally kicked a bucket, but it means somebody is going to die. It has, in its dictionary, every slang expression one can think of. We keep adding to the program’s dictionary when we hear another commonly used word or expression that merits addition. Take a phrase like “it sucks”. Under certain circumstances that means something isn’t good, but if you say, “the baby sucks”, that’s different. If there is ambiguity the program first searches out the meanings of the words it has in its memory, that for example, could fit into the anxiety scale. The
scale is divided up into six sub-scales; death, mutilation, separation, guilt, shame and diffuse anxiety. For example, it recognizes “I’m nervous and I feel guilty,” as guilt anxiety, and “I was embarrassed,” as shame anxiety. Now, the computer dictionary has learned from somebody, mainly from me, to classify every word and how it can be used. I may have missed some words or classified them wrong, but the computer, in contrast to you and me, is consistent and keeps making the same error. So the first thing the computer does is search for the meaning of each word and how it fits in the scales. If a word can be classified in several scales it registers that. Then it searches who did what to whom, because that makes a difference. After it registers all the possibilities for each word it decides how to classify and score them. It compares, adds, and tallies, all verbal statements, because somebody could say something hostile to others and to themself, as for example “I shot myself in the foot and, also shot him”. It may score some statements on several scales and it adds all the scores up. Then it compares those scores to norms. We got the norms by getting verbal samples from thousands of people for the different scales. These people were working, as well as mentally and physically healthy. And the norms are adjusted to the educational level. If you have a verbal sample from a five-year old kid and from a Princeton college graduate they’re going to be differences in cognitive function. So, the software program makes adjustments for that. It also calculates standard deviations from the norms, and tells you what they are. It’s more reliable if you have more than a five minute sample but the computer is programmed to provide a disclaimer about that. This allows a clinician to consider the diagnostic classifications derived from a verbal sample for the diagnoses in the DSM-IV of the American Psychiatric Association. That wasn’t a very good summary on my part, but it should give you a general idea.

TB: What you have in the development of the program is a logical process.
LG: Gradually, it aims to be logical.
TB: Gradually?
LG: If you live long enough you can do a lot, and I’ve lived pretty long. We did studies, years back, when we had a NIAA Alcoholism Research Center on how well we could take five minute verbal samples and develop regression formulas that provided neuropsychological tests scores from the Halstead-Reitan Cognitive Scale. The program printed out if the cognitive impairment score was more than one standard deviation from the norm.
TB: Let me go back to Cincinnati. You moved there in 1953, just before chlorpromazine and reserpine were introduced. And you were in Cincinnati when meprobamate, imipramine and the benzodiazepines entered the psychiatric scene. Central to your research was the development of
content analysis of language but you also became involved with research in psychopharmacology. How did that happen?

LG: I could say it just happened, but usually things happen for a reason.

TB: It was just couple of years after you moved to Cincinnati that chlorpromazine was introduced.

LG: A magic drug.

TB: How did you feel about it?

LG: I was very enthusiastic. It worked, it really did.

TB: But you were not involved in clinical research with it.

LG: I didn’t publish, but I was a psychiatrist at Cincinnati General and used it. As I said, it worked.

TB: Did you have any experience with reserpine?

LG: We used it, surely.

LG: What about meprobamate. Did you use it?

LG: We used all of these drugs. I was on a busy clinical service.

TB: Were you involved in research with any of the new drugs in the 1950s and 1960s?

LG: I don’t remember exactly, but I did some research with perphenazine and some of the benzodiazepines.

TB: Could you tell us something about the research you did with perphenazine?

LG: We had a busy clinical service and put several patients on perphenazine. I wanted to see whether the content analysis scales were useful. I was developing scales around that time that measure three types of hostility; hostility outward, hostility inward, and ambivalent hostility. Perphenazine suppressed all three types of hostility.

TB: What about benzodiazepines?

LG: I worked with chlordiazepoxide first. I thought that chlordiazepoxide should lower the anxiety scale scores significantly more than placebo. The major focus of my research was not as much testing the drugs but testing the scales. I wanted to know whether they measured what they were supposed to measure. But, as I reflect on it now, I certainly was interested. Later, I did studies with diazepam, lorazepam and triazolam.

TB: Did you study triazolam on sleep?

LG: No. Just generally to see what, if any effect it had on the content analysis scales. I was interested in the effects of these psychoactive medications on the scales we were developing, and in the relationship between their blood levels to the magnitude of our scale measures. I found out they were capable of measuring what they purported to measure.

TB: So, you were using psychoactive drugs in the construct validation of your scales?

LG: Exactly.
TB: Did you do any research with antidepressants?
LG: I did some research with imipramine. In one study with non-depressed patients imipramine reduced the hostility level of subjects.

TB: So, that study was done on normal subjects?
LG: Pretty normal. Then with amphetamine and a mild barbiturate we were trying to see whether these drugs could overcome what the doctor said.

TB: What did you do and what did you find?
LG: We did a placebo controlled study. After we told the patients we were going to give them a drug to make them sleepy we gave some the amphetamine, and after we told others that we were going to give them a drug that would stimulate them, we gave the barbiturate. We had devised an instrument we called Achievement Striving Scale and showed that amphetamine overcame the effect of what the doctor had said. But we also showed that there was an effect in response to what the doctors said.

TB: Have you been involved in research with any neuroleptic other than perphenazine. Didn’t you do some research with thioridazine?
LG: Yes, but later. I got involved in research with thioridazine and had some grants for that, but that research on thioridazine and mesoridazine was done in California. I studied first the pharmacokinetics of thioridazine and, then, when I got into the metabolites I detected that one of them, I think it was sulforidazine or a sulfoxide, was probably responsible for the adverse effects on cardiovascular function. Sandoz, the pharmaceutical company that made these drugs, gave me money to study thioridazine, but when I said I wanted to find out how to reduce the amount of metabolite that caused the cardiac effects, they didn’t want to fund it.

TB: Thioridazine was the first neuroleptic in which the prolongation of QT interval on the EKG caused problems. In the early 1960s a couple of patients treated with thioridazine in a mental hospital in Kingstone, Ontario, died of ventricular fibrillation.
LG: Is that right?
TB: Yes, it was quite carefully followed up in controlled studies and Sandoz knew about it. Why didn’t Sandoz want to fund your study?
LG: I don’t know.

TB: You certainly made an important contribution by identifying that the metabolite is possibly responsible for the quinidine-like effects of the drug.
LG: Everybody told me that metabolite was not pharmacologically active. I asked the head of the organic chemistry department at UCI whether she could manufacture it for me because I wanted to test the effects of the metabolite on cardiovascular function in dog experiments. She could do it for a certain amount of money, but I never was able to obtain
the necessary funds. In general, pharmaceutical companies are not very interested in trying to discover what triggers the adverse side effects of drugs. I was interested and I still am. It’s a neglected research area, in spite of the fact that it could help to avoid some adverse side effects. But the drug companies just don’t seem interested.

TB: How did you identify the metabolite that is responsible for the cardiac conduction changes?

LG: We got regular blood levels of all the metabolites from patients that were taking thioridazine. We would get EKG’s and look at those patients that had higher levels of the metabolite. Not everybody metabolizes these medications the same way, and we found that patients with higher levels of that metabolite had abnormal EKGs. Our research focused on drug metabolism and we discovered some metabolites of drugs that other people never reported. That got me pretty far off the main direction of my research but I had a young collaborator, Eugene Dinovo, out of UCLA, and he loved that kind of research. We had a great time collaborating. There should be more studies like that; it’s an open field, the study of adverse side effects of drugs and metabolites.

TB: Did you discover any other metabolite of a psychotropic drug linked to an adverse effect?

LG: No, but we had problems funding that area of research. Eugene was a bench researcher, on soft money, so I had to keep getting grants to fund him. Eugene was brilliant and is probably still working as Director of the Pathology Lab at one of the VA Hospitals. While we worked together we discovered some other metabolites which are not in the scientific literature. We didn’t try to see whether they were related to anything, because we didn’t have the necessary funds. When you have federal grants you can’t go too far off, because you’ve got a responsibility to focus on the principal goals of your research.

TB: You think some of those findings should have been followed up and were not?

LG: Yes, I want to pursue a lot of interesting things, but I have to decide my first priority.

TB: It’s unfortunate that you couldn’t pursue your research further with the thioridazine metabolite.

LG: I visited Sandoz in Basel a couple of times. I’m sure their higher ups advised them not to spend money on that line of research because they were doing all right with the drug. You can’t get a pharmaceutical company to study what triggers the adverse side effects of their drugs. I may be wrong.
TB: The thioridazine induced cardiac conductance changes are of special interest to me because we were the ones who demonstrated that thioridazine could induce prolongation of the QT interval and ventricular fibrillation in the therapeutic dose range. We published our findings, I think in 1964.

LG: I didn’t know that.

TB: Let’s get back to your research in Cincinnati. Didn’t you do some research in hypertension?

LG: I studied the effect of hydrochlorothiazide on hypertensive patients and found it had not only an effect on hypertension but also on the subjects’ language.

TB: Did the effect on blood pressure and speech correlate?

LG: Yes. Around that time it was more and more convincing to me that we had a useful and valuable measure of anxiety and hostility in content analysis. I thought I’d like to validate it some more, with respect to a combination of biochemical and physiological factors that could be measured including blood sample. At that time, there was not a good measure of adrenergic substances such as epinephrine and norepinephrine that were thought to be involved in influencing states of anxiety or hostility. We could measure only plasma free fatty acids. These are released from the liver and fat storages in response to a chemical substance that’s secreted in the blood stream, in association with the arousal of anxiety, fear or anger. So I decided to measure plasma free fatty acids, and we did a number of studies in which we showed that the higher the anxiety levels in normal individuals, the higher the plasma free fatty acids. What we were measuring in verbal samples as anxiety or fear was associated with the biological release of adrenergic substances. We did a lot of other studies using that technique. As I said, it was the only measure in those times that was available. And, we noted subsequently that if we drew blood from a subject before and after taking the five minutes speech samples, the free fatty acids went higher with their anxiety; the more anxious they were during that five minutes the higher their free fatty acids were. We also noted that in dreaming subjects, if you drew blood from them at the beginning of rapid eye movement sleep, and fifteen minutes later the higher the anxiety in the dream on my anxiety scale the higher the free fatty acids went. The article in which we reported these findings was published in *Science*. I had an interesting query in answer to that paper from a number of people. One scientist commented, “If there’s more anxiety in dreams, there’s more arousal of adrenergic substances and in some instances that could be fatal, just from a dream”. Another query I thought was amusing was,
“Why not recommend that everybody get psychoanalyzed and put an end to anxiety dreams”? I had to write back that psychoanalysis doesn’t put an end to anxiety dreams but a person might understand better what the anxiety was about.

TB: You certainly did more than simply correlating anxiety with plasma free fatty acid levels.

LG: We confirmed that anxiety measured from language was associated with physiological, neurobiological and biochemical concomitants in the body and wasn’t just a matter of the mind. When you ask me these questions, I get a flood of memories. We noted that people in Cincinnati that were into sports, had all around lower plasma free fatty acids, than people who were not involved in sports. That’s a popular belief now that a certain amount of exercise is good for the body, as well as for the mind. I do recommend to patients once in awhile, “Healthy Body, Healthy Mind.” There’s something to it. We looked at blood cholesterol also and found that the higher the hostility scores, the greater the blood cholesterol in normal subjects. There is no paper published on that but, there is a lot of preoccupation these days with elevated cholesterol. In the 1960s, we didn’t look at whether LDH or HDL cholesterol was elevated. We were just getting total cholesterol. I don’t think clinicians were thinking very much about other factors in those days.

TB: So, you were very involved over 30 years ago in measuring cholesterol, free fatty acid and triglycerides?

LG: Yes. That was part of being in the Cincinnati environment. As I said, there was lots of interest in psychosomatics; we were looking at what effects emotions have on the fatty acid and triglyceride metabolism. I haven’t gone back to that area of research since Cincinnati, but I noticed that in the current literature, there’s some interest in it.

TB: Did you study the effect of drugs used in the treatment of anxiety on cholesterol, free fatty acid and triglyceride levels?

LG: We did that in the course of our research with the β-blocker, propranolol.

TB: What did you find?

LG: I found that β-blockers do, indeed, decrease anxiety levels in content analysis scales, and decrease plasma free fatty acid, but not significantly. Since I was seeing these responses, partly as a measure of the peripheral autonomic nervous system, I concluded that anxiety was primarily a central nervous system phenomenon. Of course our findings didn’t prove that it couldn’t be peripheral because we used a β-blocker that doesn’t go through the blood-brain barrier. Anyway, our paper on propranolol attracted the attention of Bayer, a large German pharmaceutical company, and I was invited to an international meeting of
cardiologists in Venice, where I presented our findings because cardiologists were interested in the details. It was a marvelous experience. Later, my presentation was published in a book chapter on β-blockers.

TB: In your conclusions in the propranolol paper you said it also that the anxiety you were measuring was primarily a central nervous system phenomenon but you couldn’t exclude the possibility that it was peripheral. Can your content analysis of language differentiate between fear and anxiety, or between two kinds of anxieties as some people do?

LG: I don’t think my content analysis differentiates anxiety, which is sometimes called “neurotic fear,” from “genuine fear”. It’s measuring arousal whether it is neurotic or real fear.

TB: So, it gives a single measure of anxiety.

LG: Yes, anxiety and fear.

TB: Let me shift to another interesting project you did in Cincinnati. This is your study of neuroleptic withdrawal in chronic hospitalized mental patients.

LG: It was difficult to do that study, but we did it at Longview State Mental Hospital that had a lot of chronic schizophrenic patients. I got the hunch that some of those schizophrenics seemed pretty normal to me after they had been there about ten years. I think it was the beginning of the time when it appeared there could be adverse effects in patients due to chronic administration of phenothiazines. So, I wondered what would happen if we discontinued them in a group of patients. To do that we had to get the hospital’s cooperation and I succeeded. I did the study with 75 patients and found that maybe a third or a half remained about the same or seemed even better, more collaborative. At that time, I was developing a scale for measurement of the severity of schizophrenia. I named the scale, Social Alienation-Personal Disorganization Scale, SAPD. We employed this scale on patients before and after withdrawal of the large amounts of phenothiazines they were on, and found out that those patients in whom the SAPD score before taking them off the phenothiazine was low were OK if you discontinued medication, whereas patients whose SAPD scores were well above that got very significantly worse. Our findings were of considerable interest at that time. It demonstrated that not all chronic schizophrenic patients had to be kept for the rest of their lives on a major tranquilizer. So, we discontinued the old practice, and a fair number of patients who were off medication for a while could be discharged.

TB: You found that maybe as many as 50% of hospitalized chronic schizophrenic patients probably did not need to be kept on their medication. That was a significant finding.
LG: Exactly. There are either different kinds of schizophrenia, or different levels of severity.

TB: The number of patients you took off medication was around seventy?

LG: Yes, 75 patients.

TB: Did you take them off suddenly or did you gradually decrease their medication?

LG: Abruptly, but we substituted their psychoactive medication with a placebo. It was not easy to do because the hospital personnel, especially the nursing staff, didn’t want it done.

TB: Was there any withdrawal effect?

LG: No, we did not see any withdrawal effects.

TB: So you found a relationship between the level of disorganization measured by your instrument, and a need for phenothiazine medication.

LG: Yes.

TB: How did you measure “disorganization” with the scale?

LG: If somebody giving a five-minute verbal sample did blocking, that is started a sentence and didn’t finish, that was scored. Not just content, but also the form of speech was evaluated. If they made bizarre statements, like “I saw somebody walking on the ceiling last night,” or articulated paranoid tendencies it was also scored. Verbal items that trained psychiatrists typically use to make a diagnosis of schizophrenia were scored on the scale. The SAPD scale overlapped, later, with another scale that we developed for depression. After all, some people with bad depression can be delusional.

TB: Do you think your scale picks up positive symptoms, or negative symptoms, or both?

LG: When we developed that scale we found there wasn’t a big distinction between picking up positive and negative symptoms; I’m not absolutely convinced they the distinction is important, but if it is, my scales could probably be broken down to differentiate between positive and negative symptoms. I could possibly determine whether there is any difference but haven’t got into that. The trouble with that distinction is that some of the negative symptoms might be related to personality characteristics and not necessarily schizophrenic features. For example, if somebody had a head injury, or an addiction, or a lot of shock therapy, I think that might produce some of the findings that are associated with negative symptoms. I’m not sure. And, if I were to study positive and negative symptoms I’d want to get PET scans or MRIs to see how the patients differentiate. There has been data along that line. I think Andreasen and others have shown some differences in the brain.
Louis A. Gottschalk

TB: You went as far as your instruments let you go. You didn’t have MRI at the time.

LG: We didn’t have MRI, CT or PET.

TB: This was the Cincinnati period of your career. You were involved in many things and dedicated much of your time to research.

LG: I also had practice, I was a training and supervising analyst, and I had grants. But it’s true, I dedicated a lot of time to research.

TB: You moved to Cincinnati in 1953 and stayed there for almost 15 years.

LG: I left Cincinnati in 1967.

TB: Then you moved to California, Irvine to become the Founding Chairman of the Department of Psychiatry and Human Behavior.

LG: I took the position as Chairman and there was, immediately, a very large administrative responsibility to get an approved residency, to recruit residents, to worry about all the financial problems in running a hospital. We had an emergency room that saw a thousand patients a month. I kept convincing myself that I had to continue to do research, so I knew what my identity was.

TB: So all through the Irvine years while you were building a department you continued with your research.

LG: I kept doing research and applying for grants.

TB: For how long were you the Chairman of the department?

LG: About eleven or twelve years.

TB: What percent of time could you spend in research?

LG: Twenty-five percent.

TB: What about clinical practice?

LG: You were allowed two half days a week to practice. You didn’t have to do private practice; you could do none, if you had a ceiling to your salary. At the University of California the pressure was to publish papers. I didn’t have a problem there; they have a very fine university system. It is definitely a research university, whether it’s humanities, physics or medicine. It rewards research; it was my type of university.

TB: What about teaching responsibilities?

LG: I tended to do more of my teaching with residents, rather than medical students. I did give a few lectures, but I hired people to teach medical students. I had to build a department from scratch so I worked up a big residency program. I had fifty or sixty residents.

TB: And you said that you had to spend time writing grants to generate funds for your research?

LG: The University of California was set up for the kind of research I was doing so you didn’t always need a grant. I had a lot of residents who wanted to do research, to get speech samples on various topics. But if
you want to do certain kinds of research and want to get a lab, you have to get big grants and I worked for that. But, in between, I was always able to do research. There was a period of six to seven years when I had large contract grants from the National Institute on Drug Abuse that profoundly affected my activities. While serving on different committees of NIDA, and the NIAA, I discovered that there was no uniformity across the United States in the way psychoactive drugs were evaluated by medical examiners or coroners. So I began a project NIDA supported for six or seven years, to develop a uniform system measuring all the variables in drug-involved deaths. We had a team that developed a uniform system and made recommendations.

NIDA also gave me funds for a lab where we could check some of the coroners’ findings. The data from the studies we did in the laboratory and the information I got from coroners and medical examiners has been stored away. But based on that, in collaboration with Robert H. Cravey, the head of the toxicology laboratory of Orange County, we wrote a book on Toxicological and Pathological Studies on Psychoactive Drug-Involved Deaths that was published by Biomedical Publications, in 1980. The book provides the blood levels, lung tissue levels, and all other relevant tissue levels in poisoning and death due to benzodiazepines, opiates, and similar drugs. Many coroners in this country are using our book. My research team and I also had another publication in 1977 that was prepared on request by the National Institute of Drug Abuse, (NIDA). It is a Guide to the Investigation and Reporting of Drug Abuse Deaths. My co-editors of that book were: Frederick L. McGuire, Eugene C. Dinovo, Herman Birch, and Jon F. Heiser. It was published by the U.S. Government Printing Office.

TB: So, that book was focused on identifying the drug that caused the death.

LG: There are interesting legal cases in which it is difficult to determine whether the cause of death was a morphine overdose or too big a shot of insulin injected later. There are interesting cases and a wealth of material for any mystery writer. I don’t believe the ACNP ever looked into that matter. Why should it? The drug companies aren’t interested in such details. However, I did get involved in this area and I don’t regret it. It consumed a lot of my time, but was, I think, a very worthwhile adventure.

TB: There was that famous case of a wealthy woman who was killed by her husband with insulin.

LG: Yes.

TB: Were you involved in any way in that insulin overdose death?

LG: No, but I’ve been quoted on the possible cause of Marilyn Monroe’s death. The findings are given in our book. The question was whether she overdosed or whether she was killed by the Mafia through an injection
in her rear end. I don’t want to go into all the details now. Somebody wrote a book suggesting that the cause of her death wasn’t suicide, that she might have been killed. I think the experience taught me that when somebody takes a drug, it doesn’t have to go just to the brain; it gets all through the body, the liver and everywhere else and pathologists should look to see what the levels are in different tissues.

TB: And while you were involved in that project if I’m correct you were also Director of your Drug and Alcohol Center.

LG: The Alcohol and Drug Research Center comes later. I came to UCI in 1967, and was Chairman of the Department for about 12 years. Then, I became head of the Psychiatric Consult and Liaison Service at the UCI Medical Center. I did that until I became the Scientific Co-director of an Alcoholism Research Center funded by the National Institute of Alcohol and Alcohol Abuse (NIAAA), that was a conglomerate of basic and clinical scientists. The main theme of our Research Center was “The Effect of Alcohol on the Nervous System.” We were looking at humans and animals; we had some powerful research people from molecular biology and neurobiology, and we worked together for about 10 years.

TB: Did you pursue your research with speech samples at the Center?

LG: The Center was getting data on cognitive impairment.

TB: So, after you retired from your Chair you did some work in consult-liaison psychiatry, and then became co-director of this Center. Didn’t you also become Professor of Sociology and Ecology?

LG: Social Ecology and Social Science. Even when I was Chairman of Psychiatry I had courtesy appointments there, because in a research university setting such as the University of California, it was useful to get cross fertilized and work in several departments.

TB: How long did you co-direct the Center?

LG: Our grant lasted for about eight or nine years.

TB: When was the Center in operation?

LG: In the 1980s.

TB: Could you tell us something about your research in the 1980s?

LG: It was in those years that I did the Reagan Study. There was a campaign debate between Mondale and Reagan. We were studying with content analysis the language used in conversations. We learned that we could study conversations if we looked at the form of speech rather than the content; for example, how many times a person repeats himself.

TB: How did you measure that?

LG: Counting every time there is a repetition of a word or phrase separated by no more than a word, phrase or clause. It doesn’t matter what the content
is. Those issues turn out to be important in older people or people that have brain injury. There are more repetitious, no question about it. It's related to age; little kids also often repeat themselves. It's sometimes related to the vocation. A clergyman, rabbi or politician will say, “I tell you, I tell you that we have to defeat...” ; they repeat themselves for emphasis.

TB: You started to say that you did the Reagan Study. How did you get to that and what did you find?

LG: About 1984, I was consulted by Gannett Publications from Washington, D.C., after I had been recommended to them by the American Psychiatric Association in Washington, They were told that I have a content analysis measure derived from speech and they asked me whether I would collaborate with them and measure the relative cognitive impairment in the debaters, specifically of Reagan and Mondale. So, they sent me the tapes and videos of those debates. In a political debate the debater cannot read a prewritten script; they have to be spontaneous and are somewhat unprepared. I received the tapes and the videos of the number one and the number two debates and looked at them myself. I didn’t have a computer program to do this at the time, and when I studied the tapes I noted that when Reagan didn’t have a script, he had to freelance to be spontaneous. And, my goodness! His scores on content analysis items for cognitive impairment were significantly higher than Mondale’s. So, I told Gannett Publications what I had found. I also asked them for the tapes and videos of some earlier debates that Reagan had with Carter. Those debates were four years earlier. When I was looking at those data, and their content in the cognitive impairment scale, Reagan didn’t look as bad as he did four years later debating Mondale. I asked myself, should I publish that? This was before the election and Dr. Bunney, who was the Chairman of the department at the time, didn’t think I should publish it. He was not worried in terms of research but he was concerned that publishing those findings might negatively bias the National Institutes of Health in receiving grants. So I asked the Dean of the College of Medicine, Stanley van den Noort what I should do. And he asked me, “How did it come out”? Well, I said, “Reagan didn’t look as good”. So, he said, “Publish it”! Well, I said, “Stanley, you’re a Democrat”. “You bet”. When I told Bunney about this he said, “Oh, well, he’s biased. Ask the Chancellor”. And the Chancellor, at that time, was Jack Peltason, a political scientist and economist, a guy that I respected. He said, “Well, I don’t know much about content analysis, was the work scientific and valid”? I said, “It was”. And he just simply said, “Publish it”. But, I decided not to publish it right away, because about that time some psychiatrists in the American Psychiatric Association said something negative about Barry
Goldwater without interviewing him. So, I waited till after the presidential election. Then I asked a colleague of mine in the school of business, to recommend a top rate non-psychiatric publication. He suggested Public Administration Review published out of Washington, DC. He also said, “I think, they’ll be glad, if it’s a good paper, to publish it”. The paper had a lot of statistics in it, but they published it. That was in 1988, I think. After it appeared there were criticisms about “this psychiatric gobbledy goop”; this guy doesn’t know what he’s talking about. But, we know what happened to President Ronald Reagan; he developed Alzheimer’s disease. I know that my cognitive impairment scales are very sensitive as well as valid. I kid about it sometimes, that it wouldn’t be a bad idea to try it on the pilot of your airplane. It will even show whether somebody is on an antihistamine, alcohol, or benzodiazepine. It’s very sensitive.

TB: Do you think content analysis can pick up early Alzheimer’s better than other tests?

LG: Well, our speech analysis is very, very simple and easy to do. I noticed that recently somebody got a test that picks up early Alzheimer’s by giving people the name of 30 objects to remember. An ordinary person can remember 15, but an early Alzheimer’s can only remember about seven or eight. My test will pick up an early Alzheimer at least as well.

TB: Was it also during the 1980s that you got involved with manganese and its possible contribution to violence?

LG: That was much later, probably in the 1990’s.

TB: What about your research with PET? When did you do that?

LG: 1990’s. It was unusual at that time for a single department of psychiatry to have a PET scan, but through the efforts of William Bunney and Monte Buchsbaum we had one. It’s very expensive but we got a cyclotron, and it almost drove us broke. Usually such instrumentation is under radiology.

TB: So you had a PET scan in the department and that is how you got involved?

LG: If you do PET scan you often have to combine it with MRI. So, I became involved in PET scan and MRI studies.

TB: Could you say something about the research you did with PET?

LG: Monte Buchsbaum was doing some research with PET in schizophrenia before he went to Mt. Sinai Medical School in New York. Dr. Bunney was also interested in doing studies with PET in schizophrenia. So I was involved in some of their research. But I had questions about the technique. As you know when you do PET you’re measuring, not just the architecture of the brain and the skull, but you’re measuring function, what’s going on in the brain. People aren’t saying anything because they’re in the machine. But even if they are not saying anything that doesn’t mean
they’re not thinking. So, how do you stop them from thinking because that might have an effect? Thinking about a love affair is different from thinking about being angry at a policeman. The conventional technique to control for that is to have the subjects engaged in pressing a button every time a light turns on. This procedure is supposed to block out random thoughts. I thought that this was a little bit naïve. So, I decided to do studies in which, instead of using this technique, we let the subject do nothing during the procedure, and then report verbally afterwards what they were thinking about while the PET scan was taken. With my technique we were able to correlate findings in the PET scan with content analysis of language.

TB: Could you tell us what you actually did?

LG: Specifically, you give an injection of radioactive glucose and 20 minutes later, because it takes about twenty minutes to metabolize in the brain, you take a speech sample to learn what they were thinking about.

TB: What did you find?

LG: We found that the subject matter you are silently thinking about makes a difference in your cerebral glucose metabolic rates. Subjects were not told what to think about, but the level of anxiety and hostility showed up in significant differences in their PET scans. We published a paper on our findings in Comprehensive Psychiatry with the title The effect of anxiety and hostility in silent mentation on cerebral glucose metabolism. But, then, I did studies to see whether the different kinds of anxiety or hostility in dreams would show up as differences in the parts of the brain involved.

TB: Did you find any differences?

LG: There are differences in PET scans when you are experiencing anxiety awake and when you are experiencing anxiety while dreaming. We published papers on our findings in Brain Science and other journals. That was the first time such papers were published. The brain is very complicated with regards to what part is involved with different emotions, and there is no another way we can study these matters at this time other than the technique I used.

TB: What about the effects of other emotions?

LG: I got interested in studying the effects of hope and hopelessness on the PET scan. We used the same technique as we did with anxiety and hostility and we found differences. We published our findings of this research in the journal, Psychiatry. I still have a paper that I think was ahead of its time. I scored normal individuals for social alienation and personal disorganization on the schizophrenia scales, and showed that the higher the scores, the more likely it is that parts of the left temporal lobe are involved. It’s interesting that some of the recent research
on schizophrenia shows that in schizophrenia the left temporal lobe is involved. But it’s also involved in normal individuals, who are not schizophrenic; the greater their social alienation and the more disorganized they are, the higher their scores for glucose metabolic rates in the left temporal lobe.

TB: What you are showing is continuity between normal subjects and schizophrenics.

LG: That is right. Rather than, here’s a group of schizophrenics and here’s a group of non-schizophrenics and they’re altogether different with regards to brain functions, there is continuity. It may be, that if you do the statistics, you would get linear continuity rather than separate, discrete characteristics.

TB: You were tackling important theoretical issues in psychiatry using statistics.

LG: Statistics have got to be used, one way or the other. I feel that science has to be on a statistical basis for assertions to be valid; otherwise they are a matter of faith.

TB: Yes, but one must have or develop, as you did, a suitable instrument for the collection of relevant data to analyze with statistics. You developed a suitable instrument in your speech analysis to show that your assertions are valid.

LG: To prove it.

TB: What would you consider your most important contribution to psychopharmacology?

LG: That’s like asking a guy with several children, which one, do you like the best? I care about all of them. You’re asking me to be objective. I think my contributions in the general field of neuropsychopharmacology are good and original. I think my contributions to the measurement of neuro-biological and psychobiological states and to the computerized content of natural language or verbal texts are very important. I think the neuro-biological studies with PET scan, or brain imaging, are important. I think, to me, they’re all my children and they’re equally important.

TB: I understand.

LG: I’m just telling how I feel about your question. You might think this guy is pretty narcissistic; he loves all his children, but I just think they’re all relevant. And I’m not a good judge. Time, alone, will tell.

TB: Do you think that your content analysis of language should be used more extensively?

LG: I don’t use the word, “should”, because people would say this guy sounds like a controlling person. But I want to point out that the system can be applied to conversation. There were people that used our method to
look at documents written before the French Revolution to see whether there was an increasing amount of hostility to the royalty of France in those years. You see, content analysis is getting more and more popular. It looks like it is much more sensitive than any other kind of psychiatric assessment. I’m having a growing conviction it’s a very sensitive, useful measure, and in time, it might even be useful for the analysis of social issues.

TB: Am I correct that you are still active?
LG: Yes. I’m Professor Emeritus and working full time in the Department.

TB: What are you working on currently?
LG: I see patients, children and adults, maybe 15 to 20 hours a week. I do research and I’m writing papers. And I’m funded right now for a research project from NIDA.

TB: So, you still have an ongoing grant?
LG: I collaborate with one of the younger professors, Jerry McGuire, who is Director of Geriatrics and who has drug grants. So, we’re getting verbal samples on some of those patients included in studies on grants for Alzheimer’s drugs.

TB: What else are you doing on that research grant from NIDA?
LG: They have asked me to develop software that will detect and measure cognitive impairment in drug abusing patients.

TB: It seems that you have been involved in a wide range of activities. Is there any area we have not covered?
LG: In science?

TB: Any other activities you are involved with.
LG: I like to do art; but I’m an amateur artist. I do a little water-color painting and I have written a novel. I’m writing a documentary now on my personal experiences in World War II when I was seeing thousands of neuropsychiatric cases. I’ve had a criticism of it from Simon Schuster. They think it’s too academic, and I’m trying to rewrite it. I’m having fun with that. Now, is that going to be an important contribution? No, but I feel it is important to put on paper that neuropsychiatric casualties in war are usually de-emphasized and perceived as in conflict with patriotism. It seems all right to get a Purple Heart or honors in the military if you get injured. But neuropsychiatric casualties and how they affect people is suppressed. There are many men and women that served in the military who were traumatized. They didn’t have a nervous breakdown, but it affected them, it scarred them, and it has long term adverse effects. It has affected their physical and mental health. Some of them die younger. So, I’m into that right now.

TB: That’s the documentary you are rewriting.
Louis A. Gottschalk


TB: You are not only Professor of Psychiatry but also Professor of Social Science. Is there anything you would like to put on record about your activities in that area?

LG: I think that psychiatry is not just biological science, but it involves a person’s behavior in society. I was active in the Social Science division of the University and, I think in retrospect, that I did a landmark study on the effect of sensory overload on behavior. I had a graduate student, Daniel E. Bates, during that period of time, with a similar interest to mine. He and I built a dome like structure; I suppose ten feet in diameter at the bottom, and put a subject in that dome-like structure lying down, looking upwards. We made a movie in technicolor with strong music and odd colors and projected that onto the ceiling of the dome. We got verbal samples from our subjects before and after the sensory overload experience. There was no question that after being in that dome for fifteen minutes they showed significant elevation on our schizophrenia scale. I published our findings in 1973 together with John L. Haer and Daniel E. Bates with the title, *Effect of sensory overload on psychological state,* in *Mental Health Digest.* There has been a lot of work done since that time in sensory gating, as that area of research is referred to now. There are some people in that situation who are able to compartmentalize events and perceptual experiences and shut things out, whereas others can’t. We used the Rod and Frame tests which indicate whether people are influenced by the frame in which the rod is placed or by surrounding events. We found that people who are influenced a lot by the surroundings are more susceptible to extrasensory overload. This research was done in the Social Science division, where I was working with graduate students. A lot of people have asked me since whether we still have that dome-like structure we built and the movie. I probably still have the movie. But these experiments are relevant to the concept of sensory gating. We did our research in normal subjects but the research interest today is whether schizophrenics have insufficient gating and are overloaded by sensory experiences.

TB: You said there is lots of interest in sensory gating.

LG: There is a friend of mine, Prof. J. Christian Gillin in San Diego, who used some of our ideas in his studies in this area of research. I think there is something to this idea of gating impairment in schizophrenia.

TB: Is there any other research you did or paper you published that you would like to talk about?
LG: I already mentioned that I contributed a paper to a book entitled *What About Interrogation?* Usually, you and I don’t get involved in interrogation. That’s not our field. But I got involved, reviewed the literature on that subject and wrote a paper on it. I was asked by the military to do that. I suppose they were interested in what happens if our soldiers get captured by the Koreans in the war and put under torture. Dr. Jolly West, who was Department Chair of UCLA, was interested in the effects of interrogation, and what should one do in that situation.

TB: I heard of Jolly West’s involvement in that area of research.

LG: After reviewing the literature I recommended taking LSD or something that makes you act crazy. They’re not going to interrogate you; if they think you’re crazy because they will believe your information is not reliable. As far as I know, my suggestions have been followed to some extent.

TB: Is there anything else we have not covered?

LG: We have done some studies on stuttering and found that risperidone reduces its severity. In the same paper we also reported that stuttering does not interfere with IQ and stutterers might be brilliant in some areas but have a certain type of cognitive impairment. There are PET scan studies that support that.

TB: Was this your last paper so far?

LG: No, my last paper is on *The detection of cognitive impairment from verbal samples.* It is about that eventually doing our sampling test from voice recognition, using some of the new techniques and technology, so the speech wouldn’t need to be typed. I would like to apply for a grant to do that.

TB: It would make it easier to do the test and would speed things up.

LG: Right.

TB: You are still active and moving ahead. Thank you for sharing all this information.

LG: It’s been enjoyable talking to you.

TB: It was a pleasure listening to you.

LG: About one of my favorite subjects.

TB: Thank you.
TB: This will be an interview with Dr. Leo Hollister, one of the pioneers of neuropsychopharmacology. We are in Nashville, Tennessee. It is April 6, 1999. I am Thomas Ban. Tell us where and when you were born and something about your childhood and early interests.

LH: I was born in Cincinnati, Ohio, in the 1920’s. I was educated in that city, which had excellent facilities. I went to one of the first college preparatory high schools, a public school, and then to the University of Cincinnati, which was sponsored by the city. Whatever educational attainments I’ve had, I owe to the city of my birth. My medical school training was about the same as everybody else’s. I’m always amazed when people rank medical schools; it’s not what the school gives you, but what you put into your education.

TB: Did you always plan to get into medical school?

LH: No, the earliest idea I had was to go into law. My stepfather was a Judge in the city and I remember, at the age of eight or nine, being placed in the judge’s seat, looking over his courtroom and being impressed by the majesty of the law and what it means to civilization. Later on, I determined lawyers spend time trying to distort the truth and physicians spend time trying to find it out. This was influenced greatly by the books of Paul de Kruif. He was a Dutchman who was a journalist and wrote books about the early adventures of scientific medicine. One was called *Microbe Hunters*; another was *Men against Death*, which celebrated the great advances made in the 1900’s elucidating infectious and nutritional diseases and medical progress in general. It seemed a great adventure to make such wonderful discoveries and have a profound impact on the lives of so many people.

TB: When did you graduate from medical school?

LH: I graduated about six months earlier than normally because the war came along and programs were accelerated. Our class was the first to graduate early due to wartime. Actually, I graduated the day before my twenty-third birthday. That gives you some idea of how accelerated things were.

TB: What year are we in?

LH: December 1943. I took an internship in medicine at the Boston City Hospital and on the way I was accompanied, as far as New York, by Mort Reiser, who later became Chairman of Psychiatry at Yale. Mort was taking a medical internship at Downstate New York.
After residency in medicine, I went into the Navy almost simultaneously with the end of the war. I was stationed at a naval hospital in Portsmouth and one of our officers said the war would be over in two weeks. We were still island hopping in the Pacific so I bet him ten bucks and he won. He must have had advanced knowledge of the atomic bomb and that changed things drastically. My naval career was totally undistinguished. I was stationed in Hawaii; it was the first vacation I’d had in years with very little responsibility and a beautiful place to be.

TB: You finished your residency in Internal Medicine?
LH: After military service I finished residency and started a private practice, but being a member of the Naval Reserve, attached to the Marines, I was summoned back in 1950, when the Korean Conflict broke out. Again, I had a pretty soft posting assigned to the Naval Hospital in Oakland, across the bridge from San Francisco, where I lived.

TB: So, by 1950, you were in San Francisco?
LH: I’d gone there after the war to finish my training; having passed through on the way to Hawaii it looked too good to pass up. I wound up with a wife, who was a native Californian, and produced four children. That became my home for almost forty years.

TB: Did you go back to practice after the military?
LH: No, having decided that maybe I would be called back to the military every four or five years, I thought I’d play it safe and join the Veterans Administration. There was a chap, who had a job at the VA Hospital in Menlo Park, near where I lived, and I had a job in San Francisco, where he lived. We decided to switch. He was internist for a psychiatric hospital, a totally new experience for me. I thought it would be similar to practicing veterinary medicine, because you couldn’t get reliable histories and we rely on that for diagnosis and treatment. So, it was an interesting experience. While I was there, a detail man from Ciba Geigy said they had a new drug they thought might be good for high blood pressure. Oddly enough, that had been one of my major research interests. I never published but I’d done a lot of trials with different drugs to treat hypertension and nothing worked. So, I said, “I know all the hypertensives in the hospital. If you give me some of the drug, I’ll be happy to try it out”. Things were so informal in those days that all he had to do was go to his car, fetch a few cartons of tablets and give them to me. Two days later, the first patient was started on reserpine. It didn’t take long or many patients to find out that it was the first effective anti-hypertensive. So I was impressed. When he came back three months later he said, “We now have evidence from a specialist on hypertension in Boston, that this might be good for psychiatric patients, mainly, schizophrenia”. I said, “Gosh, let’s see what
we can do”. Not having any training in psychiatry I didn’t feel confident to evaluate a drug in any kind of mental disorder, so I went to the Chief of our Psychiatric Service and told him the story. Somewhat patronizingly he said, “You know, in psychiatry, drugs have come and gone over the years and they all turned out not to be very effective. I think it would be a waste of time”. I had a streak of obstinacy so I said, “Do you mind if I ask my golfing buddies, who are psychiatrists on staff, if they would take a look and tell me what they think”? He replied, “No, go ahead”. So I asked a colleague to send patients to my medical ward; I would begin treatment with reserpine or placebo, randomly, and send them back to him for observation and evaluation.

TB: So, you did a placebo controlled double-blind study?
LH: That’s right, the first of its kind in schizophrenia. At first, we didn’t know what the proper dose was, because the only paper relating to reserpine in schizophrenia was a short paper by Nate Kline, with not very striking results, using the same doses given for hypertension. It turned out later on that Ciba decided the dose needed to be much higher. They had sent a physician from the East Coast to arrange studies on the West Coast for hypertension and any other indication. Based on the results I would start patients on five milligrams by intramuscular injection for three days, follow it up by oral doses of the same magnitude for another few days and then taper it down to three milligrams by mouth before sending them back to their ward on active drug or placebo.

TB: Are we in 1955?
LH: This would be probably late 1953 or early 1954.
TB: So, it is before Heinz Lehmann’s paper on chlorpromazine?
LH: I think it was the same time. The first study we did in hypertension was in the latter part of 1953, followed by the ones on schizophrenia in early 1954. My friends were saying, “I don’t know what the hell you’re doing to these patients, but something is going on. They’re vastly different from how they’ve been before”. Others seemed to be unchanged. In those days, the American Medical Association annual meeting was a big affair and there was a scientific exhibit on chlorpromazine by Mark Altschuler from Harvard. Altschuler was a professor of medicine. I’d read stuff he’d written, a nice review on pulmonary edema and other medical topics, but I was curious how he got to study chlorpromazine and schizophrenia. It turned out that, tragically, his wife was afflicted by the illness and that encouraged his scholarly interest. He and one of his residents had an exhibit reporting on two patients treated with chlorpromazine. I remember talking to Altschuler and asking him the details. Again, things were ridiculously simple in those days. I simply contacted Smith, Kline and
French (SKF), and said I'd like to have chlorpromazine to try in patients and, in no time at all, I had an adequate supply of both chlorpromazine and placebo.

TB: So, you did the first placebo controlled parallel design studies in schizophrenia, with both reserpine and chlorpromazine?

LH: I think so. Joel Elkes had done, unbeknown to me, the first crossover study, but mine was the first parallel group design ever used blindly.

TB: The psychiatrists who evaluated your patients were totally blind?

LH: Yes.

TB: Before switching to chlorpromazine hadn't you done other studies with reserpine?

LH: Yes, a year or two earlier. Nate Kline, who always had original ideas, some rather far fetched, decided that if reserpine was good and chlorpromazine was good, the combination would be better, which sounded reasonable.

TB: Am I correct, that you also studied the effect of reserpine in normal subjects?

LH: Yes, along with the studies in schizophrenia, I was curious how it might affect normal people. As I recall, we got 19 normal subjects. Half got one milligram of reserpine a day for a week and the others got placebo. The placebo people complained of the trivial things you expect with placebo, but the ones who got reserpine felt like they had the flu with mild diarrhea, which was one of the side effects of the drug. But the most striking thing was that 7 out of 10 developed depressed feelings. I reported that along with the early experiments of reserpine and chlorpromazine in schizophrenics.

TB: People talk a lot about reserpine and depression, but when one looks at the literature, you are one of the few who published findings.

LH: I was curious about that.

TB: It seems that what you saw was not clear cut depression.

LH: I guess we'd call it dysthymia these days.

TB: Technically, for the psychopathologist, it would have qualified as dysphoria, feeling lousy, and not for dysthymia which is having a depressed mood.

LH: Nonetheless, it was easy to see how reserpine developed a reputation, not only in psychiatric patients, but also in hypertensive patients, of being able to produce depression. There were several case reports of people committing suicide. People who are hypertensive tend to be depressed regardless of what they get.

TB: Reserpine and depression is a tricky issue. In some countries, such as Argentina and Hungary for example, they even used reserpine in low doses in the treatment of “neurotic depression.” Michael Shepherd, I
think with Davies, found that in low doses it was an effective treatment for those patients. When did you first publish your findings with chlorpromazine and reserpine?

LH: I got an invitation to the AAAS Meeting, which was held traditionally in Christmas week and in 1954 was to be held in Berkeley, which was close by. So there was a chance, for the first time, to publicize my work. At the AAAS Meeting, I gave a paper reporting on the studies we did with reserpine and chlorpromazine.

TB: So, you reported on findings in several studies at that meeting.

LH: In one paper. I always tried to be economical. In those days I was terribly naïve; I thought I was giving a paper in public and it was going to be published so that’s all I needed to say. So, I made no more mention of it. The paper was given at the end of 1954, and the book that had the paper in it appeared sometime in 1956, about a year and a half later, which is the way books are. And, of course, it wasn’t read by many people. I don’t know what kind of printing they had, but it couldn’t have been very large. If there was a way to keep your “light under a bushel”, I was doing it. I think that the book was edited by a young chap named Jonathan Cole, who was a protégé of a famous neurophysiologist, Ralph Gerard, from the University of Michigan. Gerard was a fascinating guy. He was one of these short pyknic individuals, with a round bald head and cherubic face. He always had a quip, some joke, but he’s most famous for the line, “Behind every twisted thought, there’s a twisted molecule.” It was through his pressure that the Psychopharmacology Service Center was set up as a branch of the National Institute of Mental Health and Jon Cole became the first Director. I’m not sure of the details but I think that this is generally true.

TB: So you first presented your findings with chlorpromazine and reserpine at the AAAS meeting in Berkeley?

LH: I’d been working in a vacuum, almost totally by myself, until at that meeting I ran into people who were in the field. I remember Dick Roberts from Ciba accompanied me to the Berkeley meeting and he recognized Nate Kline heading toward the podium. So Dick introduced me to Nate. Nate’s attitude toward both of us was like we were peasants beseeching the emperor; I was put off by it and remember saying to Dick, “Who in the hell does that son-of-a-bitch think he is? Does he think he’s going to get the Nobel Prize for using your drug”? Well, that wasn’t so far fetched. Two years later, he did get the Lasker Award. It may be he wasn’t so off the mark but that was a disagreeable beginning. That was a rocky relationship Nate and I had over several years. Sometimes we were friendly; sometimes we had almost ad hominem arguments. Nate was a strange
person. He always had this chip on his shoulder and he’d never miss a chance to get into an argument, even if there was a way to find some resolution. He was, of course, tremendously ambitious, which I guess we all were. That’s not to fault him, but he would pick up any little idea and immediately follow it. I remember something came up from someone that copper oxidase enzyme in blood was increased or decreased in schizophrenics and Nate immediately studied it and wrote a report. A year or so later, we found it wasn’t changed at all, wrote a report and that was the end of that. Nate was always willing to go out on a limb to be first and that was a manifestation of his great ambition.

TB: Anyone else you would like to mention who participated in that meeting?
LH: I ran into Murray Jarvik, who was there to talk about LSD. Somewhere in the history of psychopharmacology the Abramson Group seems to have been lost. You hardly ever hear of them. Murray was part of the group led by Abramson in New York, which used to get together every Friday night, and after an elegant meal, they all took LSD, did some tests while on it, and on Saturday, they’d write papers on the different effects of LSD on the various tests. There were about seven people in that group and Murray was reporting on that. Nicotine later became his major drug of interest. Another chap at the meeting, who later became a drinking buddy of mine, was an Englishman, named John Kinross-Wright. He wound up in Houston, Texas. John was a really adventurous type. His idea was if a little bit of medicine is good, than a whole lot has got to be better. He set the course record on giving chlorpromazine to people; I believe it was six grams a day. Anyway, John did do a lot of pioneer work and as a result of his aggressive treatment he probably described the first case of neuroleptic malignant syndrome. But at that time it wasn’t recognized as an entity; I think he referred to it as an acute mid-brain syndrome. John was also very imaginative. So, those two people stand out in my memory.

TB: You had done two placebo controlled studies; in one you found reserpine and in the other chlorpromazine better than placebo. Did you see any difference between the two drugs?
LH: Well, the general feeling seemed to be that chlorpromazine did it a little better, a little more quickly and a little less noxiously. You didn’t get that flu like syndrome with chlorpromazine that you did with reserpine although chlorpromazine wasn’t easy to take either. Then, of course, there was also the fact that there was no commercial advantage to reserpine. You couldn’t patent a natural product, but you could patent chlorpromazine.

TB: How did you get to the idea of giving reserpine to normal subjects?
LH: I was always curious as to what drugs do in the absence of pathology, so that’s why. Because of my interest in medicine I was also interested in
side effects. I had seen the first cases of acute dystonic reactions in this country. Maybe I didn’t see the first ones, but I recognized them. It was my custom at the time to start off with parenteral medication then switch to oral and we were working with the second phenothiazine SK&F had, which was Compazine (prochlorperazine). I started three young patients on it with an IM injection in the morning and by evening, when I was leaving and while I was at the nursing station, one of the new subjects came up and said, “Ahhhh, I can’t talk”. I’d never seen this before and nobody else had. I looked at the nurse and I said, “Well, what do you expect? He’s crazy”. I thought it was some sort of a bizarre hysterical reaction. In those days the all purpose drug was phenobarbital, so I ordered it. I called back a couple of hours later after I got home, and said, “How’s the guy doing”? I got the answer, “Fine. It’s all subsided”. So, it seemed definitely to be a reaction to the drug. One of the advantages of being in a medical area, where there’s a tremendously good medical library, is you can find out what’s been going on if you really want to. So, I went to the Lane Library at Stanford and there was an article in Nervenarzt, a German neurological journal, about a year before, which told the whole story of acute dystonic reactions, covering everything. After I read that, again in my naivety, I thought once it’s in the literature it becomes generally known; there’s no use reporting any more, because it’s all there. Of course, it wasn’t and up until ten years later, there were still case reports of dystonic reactions appearing in the literature. But, it was that sort of thing that would attract me.

TB: When did you work with prochlorperazine?
LH: This was about 1956. SK&F, for commercial reasons, decided to promote that drug as an antiemetic.

TB: In Canada, it was marketed as an antipsychotic. Did you do the same kind of placebo controlled parallel design study with prochlorperazine as you did with chlorpromazine and reserpine?
LH: We were starting, but I don’t know we ever finished that study, because when SK&F decided to go the antiemetic route, I abandoned it. It was a perfectly good antipsychotic, the reason they abandoned it was commercial. They didn’t want to compete with their own product, trifluoperazine they were developing. Until ten years or so ago, Compazine was a major antiemetic drug. Now, it’s been superseded by a number of others.

TB: During those years you picked up and reported on several side effects with psychotropic drugs.
LH: Over the next several years we had a number of papers on side effects. One of the first was hematemesis and melena, associated with reserpine. And, while one could make a case that reserpine could produce peptic
ulcer, because of its parasympathetic activity, my impression was that these were gastric erosions due to increased acid. You could get a good bleed from them, but they were not the kind that continued and gave a lot of trouble. Later on, we had a report on unexpected asphyxiation associated with a number of these drugs. I was called to see one patient in the night and he didn’t have any signs of life. The idea that he died of asphyxia was a reasonable one at the time, but later on we realized that it was probably ventricular fibrillation.

TB: Now, in addition to chlorpromazine and reserpine you were also one of the first in North America to work with Hydergine, an ergot alkaloid, in geriatric patients, sometime in the 1950s.

LH: Oddly enough, my first psychopharmacology paper was on Metrazol (pentylenetetrazol) in old age. I did a study on oral Metrazol, which was considered to be an analeptic drug. Now we’d call it a GABA antagonist; it didn’t work. Then we did a study with Hydergine (ergoloid mesylate) and had very good results in two patients; the others showed no change. Both of these patients had hypertensive brain disease, which we now call vascular dementia. I’ve often wondered why people don’t think more of treating the vascular component of dementia. It used to be that vascularization accounted for about a third of old age dementias whereas now it’s only ten or twelve percent because of the better treatment of hypertension. The vascular component is treatable even with anticoagulants or Aspirin or any number of antihypertensive drugs. All of these are probably simple, safe and relatively effective treatments. They’re not going to affect a lot of patients, but they might benefit some. I think this accounts for the occasional anecdotal experience, when somebody says, “Gee, I put my grandmother on Hydergine and she did wonderfully”.

TB: Anything else you like to say about Hydergine?

LH: I was and I felt much more confident to be a judge of the effect of Hydergine on psychosis in the aged than about the effect of reserpine and chlorpromazine in schizophrenia. I don’t remember other people working with Hydergine at the time but I remember several working with chlorpromazine.

Yesterday, thinking about this interview, I remembered one of the neglected names in psychopharmacology is Nathaniel Winkelman. He published, in JAMA, the first report on chlorpromazine in schizophrenic patients in the US.

TB: What is the story?

LH: I’ll tell you the story. Winkelman was son of a prominent Philadelphia neurologist and neuropathologist. He was a straight out psychiatrist of the time; SK&F, when they got chlorpromazine, was just a small company
and weren’t prepared to do any kind of scientific study. So they decided they’d get a psychiatrist to look at this drug. They found Winkelman and persuaded him to try it because he was local and they could keep their hand in. And, that’s how Winkelman got to study chlorpromazine first.

TB: Another early investigator of chlorpromazine in this country was Kinross-Wright.

LH: I don’t think he was as early as Winkelman who had the pressure of SK&F behind him to get published. I don’t remember the cause but Winkelman died very early in life and that’s why nobody’s ever heard of him; but he left his mark as the first who tried chlorpromazine here. SK&F had only one drug. Since 1937, they had dextroamphetamine and they were making a living on just that.

TB: What did they sell it for?

LH: Initially, as an antidepressant, I think. It wasn’t too long after when some pediatrician found it was good for the hyperactive child, so that indication came along pretty early. Appetite suppression also came along quickly. So, there were a number of indications. Gordon Alles, the pharmacologist who rediscovered it, because it was synthesized back in 1898; he had a patent on it and became the largest stockholder in SK&F. He was a big philanthropist in Southern California, making all his money on one drug.

TB: In addition to reserpine, chlorpromazine, Matrazol and Hydergine didn’t you also work with meprobamate in the mid-1950s?

LH: I picked that up around 1956. I remember I paid a visit to Frank Berger and heard the whole story; how they were looking for a long lasting form of mephenesin, and put two carbonic acids on either end which prolonged its action. I got a little booby trapped by that. I thought it’d have a more specific activity than the barbiturates, but it didn’t have anything special.

TB: What population did you use it in?

LH: I decided to try it in schizophrenics; that had become my major interest. We gave as much as forty-eight-hundred milligrams a day, which puts you at a great risk of dependence. Later on, I did a formal study of meprobamate dependence. We did see improvement but it was more on the behavioral side. What I saw, and probably misled me, was the same thing we see today when we use benzodiazepines to curb disturbed behavior in schizophrenic patients, while using the antipsychotics to work on the psychosis. It wasn’t that meprobamate didn’t help, but it was not effective as an antipsychotic.

TB: It wasn’t as effective as chlorpromazine or reserpine in that population. Weren’t you the first to pick up withdrawal reactions with meprobamate?
LH: We did a study with high doses as I said up to forty eight hundred milligrams. People could not go any higher without becoming ataxic. It turned out meprobamate produced a classical withdrawal reaction, the same thing that had been described by the group in Lexington a few years before, with short acting barbiturates. We were using simple chemical measures for plasma concentrations and calculated the half life was about eleven hours, which would put it in the same realm as short acting barbiturates. For practical purposes, meprobamate had the same kind of withdrawal reaction as the short acting barbiturates and we applied about the same increment in dose to produce it. I don’t think it ever became a major problem in clinical use because most people thought twelve-hundred milligrams was a sizable dose.

TB: Then you became involved with the collaborative Veterans Administration studies, didn’t you?

LH: The VA had a history of doing collaborative studies, dating from the end of World War II, when streptomycin and other drugs, like isoniazid and iproniazid, came along for tuberculosis. In those days there were hospitals diverted to treating tuberculosis patients in a sanatorium. There were hundreds of patients languishing there, sometimes on eighteen months of bed rest. It’d kill me. I don’t know how you could do that. So, the VA and the Armed Forces developed a set up around 1946 or 1947 to study these drugs in tuberculosis. They used the double-blind technique, derived from a clinical pharmacologist at Cornell, called Harry Gold. Cornell used to have wonderful conferences on therapy that Gold produced; they were published periodically and would discuss the treatment of different medical problems. Gold was always harping on the need to do double-blind studies. In those days, he was a voice in the wilderness, because no one cooperated, but with the VA/Armed Forces study of the anti-tuberculosis drugs, double-blind studies became much more acceptable.

TB: Were you involved in studies with iproniazid?

LH: No. I’d had a little experience with iproniazid but unfortunately, in the first-three patients we treated, we had a case of jaundice and I did a liver biopsy and showed it was typical parasitical jaundice. I remember Dr. William Middleton, the Chief Medical Director of the VA came by; he was a fascinating man, tremendously interested in every aspect of medicine and he would go into backwater places like ours to find interesting cases. I pulled up a slide and told him the story and he was very fascinated.

TB: So, you were not involved in studies with iproniazid?

LH: No, but the VA decided these drugs were important and needed to be looked at, so they asked every psychiatric hospital to nominate somebody
to go to the central office to discuss this. Our administration decided that they’d send the Chief of Psychiatry, the same guy that told me that it would be waste of time to study resrepine, to get lost, as our representative. That didn’t work and the next meeting, a few months later, they specifically asked for me to come and from that point on I became closely allied with the VA collaborative studies on chemotherapy and psychiatry. That was an eye opening experience because even though I had met people like Kinross-Wright and Nate Kline, psychiatrists in the field, I had never been exposed to a great number of other people that were important. For instance, I knew nothing about psychometrics and statistics. All of these things were fairly new but I got to meet Maury Lorr, who developed one of the first major scales for evaluating psychiatric patients, the Inpatient Multidimensional Scale (IMDS) later refined by John Overall and Don Gorham into the Brief Psychiatric Rating Scale (BPRS) which became the most popular rating device in psychiatry. I got to meet at those meetings a number of biostatisticians. I had contact with one on a follow-up study I was doing on rheumatic fever, a chap from the National Academy of Science, I can’t think of his name right now. I got exposed to lots of statistics, descriptive and not inferential. This was something new to learn. At the same time, I had good ideas about design and as a result there were a series of large scale Veterans Administration studies involving a number of phenothiazines in schizophrenic patients and ultimately one on antidepressants as supplements to try helping what we now call negative symptoms, patients that don’t show much motivation. The very first study was quite encouraging. We had four treatments; chlorpromazine, mepazine, not widely used but thought to be good because it didn’t have many side effects, a positive placebo, phenobarbital, and an inert placebo. That study came out extraordinarily well. You couldn’t have written the script any better; chlorpromazine was clearly effective, more so than any of the others. Mepazine had some effect, more than phenobarbital, and inert placebo did nothing. We were able to differentiate between two effective drugs, one good and one not so good, and I thought that was a good level of sensitivity.

TB: The studies of the Veterans Administration with antipsychotics preceded the NIMH Collaborative Studies.

LH: These were the first major multi-clinic studies and we had done two or three of them before the Psychopharmacology Service Center decided to do theirs. There have also been a few States that have done studies. I think California had one, and I’m not sure that Fritz Freyhan didn’t do one in Delaware. They were all modeled after the VA studies. In 1954 there were untreated patients all across the board but by 1956 or 1957, when
we began to do these studies, the drugs had already made inroads. But we were still getting a lot of new admissions. As you know, schizophrenia takes a while to develop. One of the thoughts that occurred to me early in the game was, all these guys are veterans and some of them are as crazy as can be. How in the world did they ever get into military service? I had done a great number of clinical examinations on people entering the military and I’d never let one of these guys through. At that time it was not difficult to get their military records. So I would dig them out to see what their first contact with psychiatry was. The amazing thing was, that these youngsters, age eighteen or so, like most young soldiers were anxious, so the diagnosis of anxiety reaction was perfectly reasonable. But now, five or six years later, they were clearly schizophrenic. I never reported this but I was at a cocktail party about that time and Roy Grinker was there. I mentioned this experience to him and he said, “I’ve had exactly the same experience in civilian life. These youngsters, the nervous kids, you think are just plain nervous but in a few years, they become psychotic”. That reassured me my observation was correct but I don’t think it’s widely recognized. Grinker must have published it, because he’s so well established.

TB: Prodromal schizophrenia.

LH: Yes, you’ve got the right word. There are some things in psychiatric nosology that are completely overlooked and some that become myths, like the fact that the conventional antipsychotics don’t affect negative symptoms. That’s one of the biggest myths ever perpetrated.

TB: Weren’t you involved in some nosological research with John Overall?

LH: John Overall and I had some interest in this for years. When we were starting off Smith, Kline & French said, “We’ll give you all the chlorpromazine free. You can treat every patient in the hospital”. They wanted to see what the impact was if we saturated the hospital with it. In those days we didn’t get six figure grants for doing fourteen patients. We got nothing. Everybody was clamoring for the drug, but there was no money involved. I thought that was a pretty good deal, because even at the market prices then, it would have been a fair amount of money for the hospital. I called up one of my best of buddies in the golfing world and one of the most cooperative and I said, “Roy, how would you like to have all the patients on the ward on chlorpromazine”? He replied, “Oh, my God, I’ve got so many patients now talking to me, who never said a word before, it’s all I can do to keep up with them”. If that isn’t treating a negative symptom, I don’t know what is. Some years later when that idea became even more popular, the concept that conventional drugs didn’t do much for negative symptoms, I looked over data from studies John Overall and
I had done. We had BPRS clusters and one was particularly strong in negative symptoms and another was strong in positive symptoms; if you compared them, there was improvement in both, somewhat less in the cluster with the negative symptoms, but it wasn definitely not nothing. At that time I was in California and John was in Texas. I remember calling him up and saying, “John, our data clearly indicates what I mentioned”. I said, “I think we ought to publish something on this before this idea gets more widespread”. But, John wasn’t very entranced about going over old data. He probably had the computer files tucked away so to get the data would have required some work. He didn’t have much enthusiasm and I wasn’t motivated to press it. So, we never did that, but there’s no question this is a myth and it’s all the more developed now because of the atypicals, which are another myth, but that’s beside the point. Let’s see, where are we chronologically?

TB: We talked about the VA studies and started to talk about your collaboration with John Overall.

LH: I stayed with the VA collaborative system from 1957 to about 1961. In 1960, I happened to run into John Overall at one of the VA annual meetings, and John, all of my friends are good drinkers, and I were polishing off some booze and coming up with all kinds of wild, interesting ideas. John was a very productive thinker and we decided to hook up and do a series of smaller, collaborative studies to keep up with the pace of drug development. We got grant support for that and it went on for many years. In the meantime, back in 1957, Nate had come up with the idea that combined drugs would be better and I did a double-blind study with two drugs. You could do it just as easily with two as with one, using a combination of chlorpromazine and reserpine vs. placebo. Well, it turned out the combination wasn’t better, it was worse, in terms of side effects. I must confess I didn’t give it a proper trial, because we used full doses of both drugs so it’s no wonder we got more side effects. That may have scotched the idea too early, because it died and whether we missed anything or not, I don’t know. With the advent of antipsychotics with multiple actions on receptors, I keep thinking that maybe a pinch of reserpine plus some chlorpromazine might broaden the spectrum. But, I’m not convinced these other actions mean a damn thing, anyway. They’re all still basically weak dopamine receptor antagonists and that’s where the story lies. By 1957 I wrote one of the Medical Progress articles in the New England Journal, summarizing the concerns about side effects and complications of psychotherapeutic drugs and I repeated that in 1960 and did another one in 1964, at about three or four year intervals. After that the number of new things didn’t turn up that fast.
TB: Wasn’t it about that time you did some work with thioridazine in depression?

LH: That idea came out of a very productive meeting. There were a lot of basic scientists there as well as clinicians. One of the things the basic scientists kept saying was that when they looked at antidepressant and antipsychotic drugs they don’t find much difference in pharmacological activity. Of course, we didn’t know the whole story at that time. Clinicians claimed, to the contrary, that some drugs were good for depression and others for schizophrenia. So I decided to do a study comparing both kinds of drugs in both indications. I figured no matter how it comes out, I’m going to win. So, I designed a triple-blind study in carefully selected depressed and schizophrenic patients. There were two separate studies, thioridazine, which we chose because it wouldn’t reveal itself by extrapyramidal reaction, versus imipramine. It turned out that in schizophrenic patients, thioridazine was clearly superior. Imipramine didn’t make them worse, as was the myth at the time. On the other hand, in depressed patients, it was very difficult to see much difference. In Europe, there was an idea abroad that thioridazine was useful as an antidepressant. I think we might have been somewhat wrong about that but, nonetheless, it was an interesting design, because, it was triple-blind. The result was not as productive as the basic scientists hoped but, by that time, they had discovered more meaningful differences between the two classes of drugs.

TB: Do you think that thioridazine has a place in the treatment of depression?

LH: If you had a psychotic depression, it might be the antipsychotic of choice. However, the combination of perphenizine and amitriptyline seems to work so well, I don’t think anybody proposes it. Plus thioridazine has an anticholinergic action, as well as imipramine, so if you use the combination you may wind up with a lot of patients who have paralytic ileus or blurred vision. So perhaps, it’s just as well that combination was never developed.

TB: I think you also did some work on the effect of thioridazine on the EKG?

LH: The EKG work stemmed from the question of why some people died suddenly. We found that thioridazine was probably the worst in terms of increasing the time for ventricular repolarization, that is the duration of the QT interval, and this would increase the odds, which were remarkably small, of a re-entrant ventricular rhythm leading to ventricular fibrillation. We also found that was due to the thioridazine metabolite mesoridazine. It’s surprising how much misunderstanding there is about sudden death. One of the most memorable medical papers I ever read was when I was intern and it was by Allen Morris, the Chief Medical Examiner for Boston, who had his lab at the Boston City Hospital, where I was an intern. It
had a fascinating title, *Sudden Instantaneous Physiologic Death*. He was describing deaths that occurred suddenly and unexpectedly, without obvious cause where you could find nothing post-mortem. You could only die suddenly one way, and that’s to have your heart stop. And the heart stops mostly from ventricular fibrillation although there are a few cases of sinoatrial electrical disturbance instead. That explained so many things, over the course of the years. I got interested in this problem when two lawyers talked about wanting to sue somebody because a patient was sleeping with her husband who noticed, about three o’clock in the morning that she made some movements and when he next awoke about 4:30 she was dead. Was she poisoned by the drugs she was taking, because that’s the only thing that medical examiners think of? They’ve got to find an answer for the death certificate. There are about four hundred thousand cases of sudden death in this country every year. About eighty-five percent of them are associated with obvious heart disease and there are some probably due to electrolyte disturbances. There are a few unexplainable cases and they’re the ones that medical examiners go nuts over, trying to find what to put on the death certificate. The big problem is being able to tease out the small numbers that are due to drugs like thioridazine and mesoridazine. Fortunately, it hasn’t been a major issue.

TB: While doing this research with psychotropic drugs in the 1950s and 1960s what was your position at the VA?

LH: From the time I joined Veterans Administration in the early 1950s I was the Chief of Medicine, mainly at Menlo Park, California. It wasn’t a very big position, because it was, primarily, a psychiatric hospital. But it was a rather odd title for somebody who, by the end of the 1950’s, had become fairly well known in the field of psychopharmacology, to still be called Chief of Medicine. In 1960, a new hospital was built on the Stanford campus, called the Veterans Administration Hospital in Palo Alto a few miles away from Menlo Park. This was a Dean’s Committee Hospital taken over by the faculty and staff of the University and I was really nobody, as far as they were concerned. They didn’t know what to make of me, because I wasn’t part of the official family. I was just on the clinical faculty. They had somebody else in mind for Chief of Medicine so they made me Associate Chief of Staff for Research, which meant I was responsible for meeting the needs of a lot of prima donnas for research space. As you know, most of these hospitals are built with no research space and you have to create it. Fortunately, I was an old hand in the VA and I knew how to get things done. Over the course of the first three years, during the 1960’s, we created a lot of new research laboratories for faculty members and that was one of my main responsibilities. By 1960, I guess...
the CINP had formed, but I never attended the meetings because I had a young family and didn't want to be traipsing all over Europe with them.

TB: When did you become a member of the CINP?

LH: Around 1960. About the same time I remember getting a call from Ted Rothman, in Los Angeles. I knew him as a clinical psychopharmacologist and he was in the process of starting a new society to be called the American College of Neuropsychopharmacology. He asked whether I would like to join as a founding member? I said, “Ted, there are so many societies these days and they’ve just formed a new international one. Why do we need another one”? I tried to talk him out of even starting it. Finally I said, “Well, if you want to start it, I’ll be happy to join as one of the first members”. There were two meetings in Washington, neither of which I attended. It turns out, according to the by-laws, after two meetings you miss that are unexcused, you should be booted out! Finally, I went to the third meeting which was also in Washington and punctuated by a blizzard that marooned us but it was a good meeting. At the hotel, we were checking out and Ted and his wife were nearby so I went over and said, “You were absolutely right to found this society. It’s a great one, I’m glad you asked me and I’m proud to be a member”. From that point on I don’t think I ever missed a meeting.

TB: You became President of the College. When was that?

LH: I guess, in 1973. After that blizzard, we moved to warmer climates, most often to Puerto Rico but also Phoenix, Las Vegas and San Diego. We stayed away from snow.

TB: What about CINP meetings?

LH: I attended the first meeting in 1964 in Birmingham, because my three oldest kids were old enough to travel and get something out of it. I got to know a lot of people in the CINP. One of the most impressive was Paul Janssen. I guess I was most impressed by Paul’s facility with languages; like so many educated European scientists, he could switch from French to German to Dutch and English with no problem at all.

TB: So, you met Paul first in Birmingham?

LH: In Birmingham, and I considered him one of the few geniuses I have been privileged to know. He’s a knowledgeable person.

TB: You, also, became the President of CINP.

LH: Well, later on, after a humble and reluctant beginning. I also met Phil Bradley in Birmingham, who was the host of the meeting, and later Phil came to do a sabbatical at Stanford and I saw him periodically. I remember having lunch with Frank Ayd in Birmingham who I’ve known since day one in the field. He was one of the first people I knew, and I knew of his sojourn in the Vatican, where he was an advisor to a couple of Popes.
On Christmas 1962 or 1963, my secretary was going through the mail and said, “It looks like you got a Christmas card from the Vatican”. I said, “That’s undoubtedly from Frank Ayd, if it’s not a signed picture of the Pope, I’ll be disappointed”. Well, it was just an ordinary religious Christmas card. Having lunch with Frank I mentioned this story and Frank just kept a straight face. But, next Christmas, I got another card from the Vatican. This one had a photograph of Frank with twelve of his fourteen kids and the Pope. So he got one up on me, it really floored me. My second son probably still has that photograph somewhere. It was a nice time to get acquainted on a larger scale; I guess I’m fundamentally an organization man. Every organization I’ve belonged to, I wind up being active and becoming some official. I became President of the ACNP. At that time, there had only been one US President of the CINP, and that was Paul Hoch, who was the second or third President. Since I was an authority with the ACNP, they figured I would be sort of a liaison as President of the CINP and I was honored with that. I missed very few meetings of the CINP, one in Jerusalem and the one they had in Puerto Rico. Other than that, I’ve attended all the meetings. They, too, have been excellent.

TB: You were also involved with Jonathan Cole’s Psychopharmacology Service Center.

LH: After the VA studies in 1957 or 1958, the Psychopharmacology Service Center decided to do a study and Jon asked me to be one of the members of the advisory committee on that. That’s where I first met Gerry Klerman, who was in the Public Health Service at the time. Gerry was a very impressive young man, had a lot of good ideas, and was a lot of fun to be around. Out of that came the nine hospitals Acute Schizophrenia Study, in which they recruited mainly from State hospitals. We also went to fancy places like Payne-Whitney Clinic. In those days, there was much less consciousness of mania than there is today and, undoubtedly, all these patients were not really schizophrenic, but many were probably acute mania and that may have altered the results somewhat. The study first proved that the antipsychotic drugs worked, which was no surprise. I’d always said that any idiot could tell, after you saw two or three patients, without any controls, that something was working. But, at that time, the ranks of psychiatry were very much against drugs, especially academic psychiatry, which was dominated by analysts, or analytically oriented faculty. That’s why, in the history of these drugs, it’s largely been the non-academic centers that were involved, not the big academic centers. They thought this was all a fashionable thing. So, in order to persuade people there was really something to it, we had to do impeccable controlled studies to convince them this was not wishful thinking. We had
to do what I call “massive scientific overkill”. All these elegant controlled studies proved to the skeptics that there was something to it. Now this has become a routine affair. To get something through the FDA you’ve got to do big controlled studies, similar to the early ones.

TB: Am I correct that you are saying these large multi-center studies were overkill?

LH: I think I can say this with no fear of having an axe to grind, because I was instrumental in getting that method going. Now we need to find new ways to prove these drugs that are simpler, cheaper and quicker, because to do these massive controlled studies, with a couple of hundred patients, costs tens of millions of dollars and takes about a couple of years to do. Furthermore, only people with big bucks can get into the field. If somebody has something that isn’t patentable but it works very well, you have to overcome that. So, it’s time to look for a different mode of operation.

TB: You got involved with Jon Cole’s Early Clinical Drug Evaluation Unit (ECDEU), program as well?

LH: That’s right. In fact, the government spent a lot of money establishing these ECDEU, to do just that; to take flyers on drugs that might not have a big commercial backing and see whether they worked or not. That was a good idea, but it wasn’t done in any systematic fashion. People did, more or less, what they wanted to.

TB: When did you get involved in the ECDEU network?

LH: When John Overall and I decided to split from the major VA studies and do these collaborative studies with maybe five clinics working together; we obtained one of the ECDEU grants to support that. And we went through a number of drugs and studies. We did a reprise on something I’d done earlier on chlordiazepoxide (Librium), studying possible withdrawal reactions. Around 1959, Roche was beginning to develop Librium. I had not studied it, but I was invited to a meeting in Princeton, with the investigators who had, and they were so uniform in their praise of the drug and all the patients swore by it that I said to myself, “If it’s as good as they say, it’s going to be abused”. I previously mentioned I’d done a study with large doses of meprobamate in schizophrenics so I thought I’d try similar large doses of Librium to not only study what it does in schizophrenia but, also, test the withdrawal reaction. I devised a study where we gave up to six hundred milligrams of Librium a day, after which most patients were ataxic and, then, very carefully withdrew them under controlled circumstances, measuring all kinds of typical criteria, including EEG’s and plasma concentration. Unlike the other shorter acting drugs we had previously studied, the withdrawal reactions to Librium were delayed. The first couple of days, not much happened. By the third day, people began
to get jittery and by the fifth day, they had a withdrawal reaction, which
was gone by the seventh or eighth day. From the plasma concentrations
we calculated the half life of chlordiazepoxide to be about forty-eight
hours. Later on we described an attenuated kind of withdrawal reac-
tion with Valium in one of our collaborative studies. At one of the clinics
they raised the dose of all patients on Valium without telling me to a
hundred and twenty milligrams of a day and when the drug was suddenly
withdrawn the same kind of reaction was seen as with Librium but in an
attenuated version. The fundamental conclusion derived from this was
that the onset and severity of the withdrawal reaction is a function of the
half life of the drug. We studied another meprobamate like drug with a half
life of two hours but couldn’t get anyone dependent on it.

TB: Was that drug, tybamate?
LH: It was. With phenobarbital, which had been used for many years in chron-
ically epileptic patients, there had never been any withdrawal problems
because with a ninety-six hour half life, it has its’ own tapering off action.
That principle we derived from different half life studies has remained
constant ever since and is still valid.

TB: Your idea of why there were no withdrawal effects with tybamate was
rather novel.
LH: I think it was new. As more complex drugs became available more sophis-
ticated methods were needed and in the 1960’s measuring plasma con-
centrations became fashionable.

TB: I think you were also involved in testing some of the biochemical hypoth-
eses in psychiatry.
LH: Let’s put it this way; I’ve always been a dilettante and I’ve had the freedom
to choose whatever I wanted to do. That’s probably also been something
of a disadvantage, because it hasn’t kept me following a solid line of evi-
dence, where I could develop a field entirely, but it has been interesting
because I can go where I desire. Now, a number of things have come
up from time to time that had theoretical implications in schizophrenia.
For instance, one of the earliest was the pink spot. This was found only
in schizophrenics, it was said, and chemically, it turned out to be 3, 4
dimethoxyphenylethylamine, DMPEA, a subseance with a dimethoxy-
phenyl group removed from mescaline. So, it was extremely interesting
to think this might be the endogenous psychotogen that everybody was
looking for, the chemical that caused schizophrenia. This had been pos-
tulated by Hoffer, Osborn and Smythies about adrenachrome and various
other substances. I heard that Arnold Friedhoff was playing around with
it so I decided to see what it did in man and took the first dose, which
was rather small and nothing happened. We gradually increased the dose
until it was obvious the compound had no activity, or so little that it didn’t matter. In the meantime, Arnold had been working on it in the military and found it was very quickly metabolized with a half life measured in minutes. So, we published two papers, one on the metabolism and one on the clinical aspects. That scotched that idea. Another notion was that, if the dopamine hypothesis was correct, too much dopaminergic activity might cause schizophrenia. Things, other than blocking the receptors with drugs, might have an antipsychotic effect and, to this end, we studied a drug called acetyl methyl tyrosine, which has a specific effect on tyrosine hydroxylase, the main synthetic enzyme for dopamine. Sam Gershon and I were simultaneously beginning work on it but didn’t get very far before they said we couldn’t use it in man because in dogs it produced kidney stones. It turns out dogs have a very acidic urine and this material would normally be precipitated. So it wasn’t likely to cause any trouble in man, but we had to stop. We published our results showing it had no clinical effect at all. Those were a couple of approaches to theories on what might cause schizophrenia.

TB: By that time you were also interested in chemically induced psychosis, right?

LH: That happened around 1960. I looked over the field with LSD and wasn’t keen about the work that had been done with it so far and thought I could do better. My first question with any drug is to find out what it does clinically. So, I took pains to elucidate the clinical syndrome that LSD produced. Up to that time, you could read a hundred papers on LSD and not know what it did in man. Other hallucinogenic drugs were coming including psilocybin and mescaline which was an old hand. It turned out all three were almost interchangeable, except for there was a difference in dose, with mescaline being the least potent and LSD the most. Otherwise, they were all qualitatively pretty much the same. One of the interesting questions was, did LSD produce a model psychosis similar to schizophrenia. So, we got some tapes from people on the drugs and compared them with tapes prepared with schizophrenics. Painstakingly, we edited the tapes for any references that might tip off which tapes were which. Then we asked about twenty psychiatrists to review them and all of them could tell immediately which tape was from the subjects on LSD and which the schizophrenic patients were. Then we said, let’s see if psychologists can tell. They could. Then, let’s see if nurses can do it. They could. Then, let’s see if social workers can do it. They could. So it was obvious there were major differences in what the subjects were experiencing and expressing. That killed the idea that LSD produced an honest to God model psychosis. I used to quibble
about that with Danny Freedman, who was interested in LSD from way back and did similar work with LSD. We settled it by saying that the experience might be similar in the very early stage of schizophrenia, but not in the later stages. I still think I was right, but Danny was such a gentleman you couldn’t disagree with him with much enthusiasm. He was fine, fine man. We did a lot of studies over the next six years from about 1960 to about 1966, where we looked at LSD in facilitating psychotherapy, which was one of the major claims. We used LSD, psilocybin and mescaline in various doses, taking patients who were stabilized in psychotherapy, and doing one interview with no drug, one with placebo, and one with each of the three drugs. So we had five interviews and I had a blind rater evaluate the interview content for how much useful information, psychotherapeutically, might have been derived from it. It turned out they were the same and I concluded that, if you wanted to loosen up a patient for psychotherapy, a couple of martinis would probably give you much more reliable data, because LSD, psilocybin and mescaline muck things up. So, that was one of our studies. Another study was derived from the fact that some engineer, who had become a quack in this field, was going around the country and giving alcoholics six-hundred microgram doses of LSD, which is a fairly good jolt, with the claim that after one dose you were cured. He said, you got instant insight into everything that caused you to be an alcoholic. That seemed to be too good to be true so we tried to do a control study; I thought the best control drug would be dextroamphetamine. I took the first dose of sixty milligrams, and if I hadn’t known what I’d taken, I would have thought it was the world’s best tranquilizer. Everything was working on all cylinders in perfect tune and it was wonderful. I couldn’t sleep, but who cared? So, we used that dose as the placebo and then gave them a substantial dose of LSD. We found there was no good rating scale for alcoholics. At that time, everything was, either you’re a drinker or you’re not. I thought that was a rather foolish criterion, especially when you’re trying to do a quantitative comparison. So I got some psychological help to devise a drinking behavior inventory, which touched on the amount that people drank, the effect on their personal life, their job and all areas likely to be affected by alcohol. It looked pretty valid and was able to make distinctions, but on further analysis, the major criterion for making these distinctions was how much you drank. Simply tabulating the number of drinks per day would probably have been as good. About ten years later somebody rediscovered the scale and I began to get inquiries about reprints but I never thought it was wonderful and I still don’t think there are scales that quantitatively measure how much damage
alcohol is doing. We did every study we could with LSD, and by 1966 I decided to give up on it.

TB: Weren't you also involved with STP and THC?

LH: In the summer of 1967 in San Francisco, where all the hippies were born, there was a drug on the street called STP, which the Feds were quickly able to identify as 2, 3 dimethoxyamphetamine. I was at a meeting in Washington on drug abuse reform and a chap who worked for them, named Milt Jaffe, told me about the problem with it in San Francisco. He had some in his desk drawer and gave me an armload of it. In no time at all, we found out it was identical, qualitatively to the LSD, mescaline, psilocybin group of drugs. But, unlike them, tolerance developed fairly rapidly to repeated doses and you couldn’t block the effects with chlorpromazine or antipsychotics; the notion being that if these drugs were truly inducing models of schizophrenia, then antipsychotic drugs should help. But they don't, they tend to make things worse. We had that all wrapped up and I sent a report within about three or four weeks to the Committee on Problems of Drug Dependence. They had a meeting to consider this problem, and the person who chaired it, was the dean of drugs of abuse, Nathan Eddy. Nathan was very impressed by our report and I become a member of their “committee”. This began a long association with that group which, at the time, was under the auspices of NASNRC; we met in their building on Constitution Avenue. In a couple of years, I became the Chairman of the committee, and served for several years, until the NAS wanted to reduce the number of committees and decided to “off load”, ours. So, it became my duty as Chairman to shepherd the committee from the NASNRC to an independent state. It took a lot of time and effort, but it was worth it, because the committee survives as a College on Problems of Drug Dependence, a membership organization and the most prominent, scientifically impeccable group, devoted to substance abuse.

About 1966, Mechoulam, in Israel, finally determined the true structure of THC, which was not much different from the structure of the compound Synhexyl discovered by Adams around 1940 for which he won the Nobel Prize. When THC became available, I decided it would be interesting to study its clinical effects, and to know if Synhexyl was like THC, because Synhexyl had been used in a lot of clinical studies for possible therapeutic uses. At that time there was a retired pharmacologist from Abbott, R. K. Richards, working in our area, who was able to get from Abbott some twenty five year old Synhexyl in a little glass vial that was in the freezer. It looked like a bunch of tar but we reconstituted it in alcohol and water and were able to make a hydroxalcohol solution where we knew the dose and compared it with oral doses of THC. So our first study was a comparison
between Synhexyl and THC. To make a long story short, they were very similar, the major differences being Synhexyl had longer latent periods and it was weaker. Otherwise, it was qualitatively quite similar, which gave validity to the previous work that had been done with Synhexyl. We were also able to develop the clinical effect and time course of THC on neuron intoxication and I plotted this on a time scale, graphically. Two or three years later, when labeled THC became available, Lemberger and Axelrod’s laboratory did the same study using labeled material and it was the same one we drew from clinical observation.

TB: When did labeled THC become available?
LH: Around 1965 or 1966. Harris Isbell and his colleagues in Lexington had it first, and we were the second. A chap named Andy Weil got into the game at that time. He’d just graduated from Harvard Medical School, and he’d been a botany major as an undergraduate. So he was interested in drugs in plants and embarked on a study using marijuana. His paper was published in Science, but I wasn’t bright enough to figure that this would be of interest to Science so I published my results in the Journal of Clinical Pharmacology. I must say, in all fairness and not being modest, our paper was more informative than his. Andy became propelled, all of a sudden, into the first ranks of substance abuse people, about which he knew nothing. When it came time for him to go into the military he wanted to go to the Public Health Service and they offered to send him to Lexington. Anybody in their right mind, who wants to do things in substance abuse, goes to Lexington to learn the ropes, that’s the Mecca. But, Andy turned them down. At one meeting Andy was giving his paper and I was sitting next to Jerry Jaffe who looked over at me and said, “Is this guy for real?” I replied, “you said it, Jerry, I didn’t”. So I’m not at all surprised he’s currently the big guru of alternative medicine and probably making millions of dollars, but as a scientist, he was zilch. You do run into some strange people. Anyway, that got us started on studies with marijuana, which continued until recently. I don’t think we’ve done anything for three or four years, but I’ve a couple of studies still not written up for publication and we covered, pretty much, all the aspects of marijuana.

TB: Could you review the most important steps in that research?
LH: I can’t think of all of them. We did electrophysiological studies, things like contingent negative variation and continual EKG recording. We studied the biochemical effects vs. clinical effects, over and over, using the various isomers and found out that cannabinoid and cannabionol were virtually clinically inactive and there was no interaction between them and THC. We studied a number of other interactions with THC. It was a
sizeable body of clinical work and probably the largest on THC and mari-juana that’s around.

TB: What were your conclusions?

LH: If you got a big jolt of it, you get a very rapid heart rate and conjuncti-vitis, both of which we showed were accurate in determining how long the drug was effective. The tachycardia can be a problem in people with angina, but on the whole it was very safe.

TB: Do you think it should have a place in treatment?

LH: We came to the conclusion that there are very few contraindications to using it. The evidence is shaky, but our clinical evidence suggests that if you have a history of schizophrenia or mental illness in the family, stay away from the drug. The Swedish experience suggested that there’s a more direct relationship, but I’m not sure. We did notice when patients would go on week end passes at our hospital they would often come back on Monday kind of loony, and if we did urine analyses, we’d find they had marijuana metabolites in their urine. This led to a routine practice of checking people when they came back from passes. Most of them, who had positive urines, also had some clinical deterioration. So, I don’t think it’s good for people with mental illnesses or for people with coronary disease, to have it. Probably among social drugs, it’s as safe as any, but maybe caffeine is a little safer. I don’t know. It doesn’t cause anywhere near the morbidity and mortality that nicotine, in the form of tobacco does, and certainly not as much as alcohol in its various forms. As far as therapeutic uses are concerned, the case is already made that oral THC can be effective to treat nausea and vomiting associated with cancer chemotherapy. It’s on the market and rescheduled as Class 2 for that indication. The only trouble is, the company who makes this stuff and who got a totally free ride from NIDA in developing it, charges an arm and a leg. It’s very, very expensive. If you do the same thing with mari-juana cigarettes and buy them on the street corner, you could save a lot of money. There’s no reason, pharmacologically, to believe that if the oral preparation works, the slow smoked preparation shouldn’t work. It would be on a different time schedule, because the pharmacokinetics, are different and we explored that extensively. The other possible indication is the relief of pain; nobody has any idea of how it does that, but there are enough reports that it has some analgesic effect. I expect that’s going to await the development of a synthetic cannabonoid, which may not have the mental effects, which could be patented in analgesia. There’s also some reason to believe that it’s effective against muscle spasticity, which is not very well relieved by any existing drug. So, there are some valid medical indications that need more exploration and I don’t see any
reason to think that marijuana is any different from any other drug being developed.

**TB:** Have you published on that?

**LH:** The final draft is being typed up this week and will go off to Israel next week.

**TB:** To the CINP journal?

**LH:** Sure. It probably has 200 people submitting important papers so it might help the new journal get off the ground and, secondly, they give a good review. I may not agree with all the referees, but I don’t mind telling them when I don’t, and when I do I am very grateful.

**TB:** That’s the last paper you wrote. Am I correct?

**LH:** I don’t know whether I’m going to write any more or not.

**TB:** Well, let’s just see.

**LH:** As you get older you do less original research and more review papers. I’ve got a paper coming out in the *Canadian Journal of Psychiatry* on *Calcium Channel Blockers in Psychiatry*. We did a study on that a few years back, which seemed to indicate that Verapamil was about equivalent to Lithium.

**TB:** You started to work with calcium channel blockers years ago?

**LH:** I think our study was published about ten years ago and there were weaknesses in it. First of all, the sample size was small, and you had a very good chance of not being able to reject the null hypothesis. The second thing was, I don’t know what was wrong with our patients, but none of them did very well and the results of the treatments were rather poor. But the *American Psychiatric Journal* accepted it and there were a few other reports that suggested it might be useful including a number of papers on mania, going all the way back to the early 1980’s. A fellow named Dubosky in Denver has done most of the work. Curiously enough, there’s a whole chapter on this in the new textbooks that the APA published. There have been two studies, one from Australia that indicates it wasn’t near as good as lithium, and the other one from John Davis’ group, saying that it was ineffective compared with placebo. Now, if that doesn’t kill it, I don’t know what does.

**TB:** Let me just switch a little bit. When did you start to work with lithium?

**LH:** I never did much work with lithium.

**TB:** Why was that?

**LH:** Being an internist gave me a disadvantage, because I remember in the late 1940’s, lithium chloride was introduced as a substitute for sodium chloride in patients with congestive heart failure. The idea was, you reduce the intake of sodium but, all of a sudden, a number of these people died and it was probably lithium toxicity. So, when I first heard of lithium in
psychiatry, I said that’s a poison. I couldn’t imagine it could be useful. I think Sam Gershon did more than anybody, along with Cade’s work in Australia, to popularize it in this country. I regret I had very little to do with lithium because it certainly was one of the major advances.

TB: Let’s go back to the 1960’s. Some of the theories about the mechanism of neuroleptics came about in 1963 by Carlsson and Lindqvist, the dopamine theory. You worked with haloperidol, at first, in the early 1960’s, and with some of the other butyrophenones. Is there anything you’d like to comment on in the treatment of schizophrenia?

LH: Recently, I had occasion to look at a paper I published in 1962, which I think was the first North American paper on haloperidol, and I was dumbfounded. The doses we used to produce an antipsychotic effect were two to 4 mg a day. I thought, oh my God I forgot my own lesson, because I’d been using 10 mg and had some people on massive doses and we’ve all been using too damn much. It’s interesting to think, in terms of the atypical antipsychotics, that if we compared them to four milligrams of haloperidol, instead of ten to fifteen that the differences would not be so great in terms of extrapyramidal reactions or tardive dyskinesia, but we missed the boat. There were a couple of people, one of them named Haase, who developed a neuroleptic threshold, the onset of micrographia, to determine the required dose.

TB: That’s right.

LH: They showed you could get detectable micrographia at very low doses but I didn’t believe it. They were right. We’ve been using, altogether, too much.

TB: Paul Janssen was very much for the handwriting test. In the late 1960’s, he was so much in favor one should use it, that he published a book, Neuroleptic Drugs, written, a very small part by Janssen, the rest by Haase. So there was some kind of disagreement between the real clinical needs and marketing.

LH: I remember Paul telling me that the custom in Belgium was to have it in liquid form and let the nurses regulate the dose, drop by drop, literally. They were using low doses and very small increments, but we all missed that. If we did a new study comparing the atypicals with small doses of haloperidol, it might not look as different as people think.

TB: Did you work with the atypicals?

LH: No, I’ve not worked with any. By that time, I’d long since given up testing drugs. Back when John Overall and I were working, and nobody knew what the best ways were to give the drugs, what was the best way to use rating scales or what were the best statistical procedures, it was something you could contribute that was original and scientific. Now, it’s all
become so standardized the drug companies have big groups of people designing protocols, rating scales and report forms and analyzing statistics. They come to an investigator with a protocol about that thick, all written up, including the consent form and if you say you’ll do it they ask how much? I saw a protocol the other day for fourteen patients and it cost about $140,000.00. It reduces the investigator to a mere peanut gallery, and most of the studies are done by the flunkies they hire so there’s no scientific input at all. Will they accept the investigator’s article? No, they send it out to some flack firm that specializes in writing papers and it is written impeccably by people who know nothing about the study. The names on the paper go by how many patients you’ve contributed. Well, that’s a helluva way to do things! I can’t think of anything duller. So, I gave it up years back. The last study I contracted to do I did only to get one of our new faculty member started.

TB: So, you think we are missing the boat by having a bunch of people design something, then someone else generates the data and someone else again processes it.

LH: My feeling is that any time things get standardized, that’s an excuse for not thinking. When things become routine and standard, that means you stop thinking. All the protocols now are impeccable and they sail right through the FDA. The FDA loves it, so all the companies want to do is get one or two of these multi clinic studies.

TB: Do you think that any of these atypical neuroleptics might not be different if you look at some of the old drugs with receptor assays? Do any of these new drugs contribute anything major?

LH: That’s a big issue right now. I was recently at a meeting convened by a group of mental health and mental retardation administrators and they’re getting terrible pressure to purchase so much from these new second generation atypical antipsychotics for all of their schizophrenic patients that would break their budgets. They wouldn’t have anything left for anything else, because these things cost up a hundred times as much as haloperidol. I don’t think anybody realizes how terribly expensive they are and how cheap haloperidol is. Tablets of 10 mg from generic drugs probably cost less than ten cents. You’re talking pennies versus dollars. So, there’s a big drive to petition the State legislature to appropriate fifty million dollars or whatever to buy atypicals for more patients and citizens’ groups are demonstrating at the Capitol. Some of the people from NAMI and other advocacy organizations are claiming this is a magnificent new era of psychotherapeutic drugs, we are doing patients an injustice and it would be unethical not to treat them with these drugs. Now, you know where that orchestration is coming from. It’s very well organized by
the drug companies, because they would like nothing more than to have these drugs declared first line treatments. I don’t agree with that and I tried to point out the difference, so people don’t get misled. If you had unlimited amounts of money, then sure, treat everybody with a drug that costs several dollars a day. What difference does it make if somebody else is paying for it? But if I had to pay for it, out of my own pocket, I might have a different perspective.

TB: You are still of the same mind as when you wrote a book with Ole Rafaelsen, *Psychotherapeutic Drugs An Ultrashort Practice*. When was that?

LH: Sometime during the 1970’s. It was Ole’s idea and became enormously popular. He thought of it as guide for developing countries and I forget how many languages it was in.

TB: At least ten or twelve.

LH: I didn’t think it was going to be so popular, but it was essential information which even the barefoot people in China could use and it was probably translated into Chinese.

TB: I think it was. If my recollection is correct, you said in that book, chlorpromazine and haloperidol are the two drugs you can do everything with. So you would still say that, right?

LH: I don’t work in the field of basic receptors; but the only difference between the atypicals and the older conventional drugs, if you look at the receptor profiles, is that common to every atypical is a weak blocking action on $D_2$ receptors, while serotonin blockade is variable. Besides, there’s no way of proving that serotonin blockade has a damn thing to do with extrapyramidal reactions or schizophrenia. Ketanserin, which is probably the best available $5H_2$ receptor blocker, has no effect, or Janssen would be selling it. Nobody knows what $D_1$ blockade does and $D_3$ and $D_4$ are the same story. I was talking to somebody recently, who said there’s a current study going on with a $D_{2A}$ receptor blocker showing an antipsychotic effect. If that is the case there might give some truth to the idea, but, so far, I don’t think there’s any evidence. The new drugs work exactly the same as the old ones, only less.

TB: What makes olanzapine and risperidone so successful then?

LH: Philip Seeman claims that is due to the fact they do not bind as tightly to a receptor as the conventional drugs and are easily disassociated, so they’re in and out. But if this occurs, why should they not also produce extrapyramidal reactions as well as antipsychotic effects? Well, he thinks it has to do with the rate of firing. That may be the explanation. Of course, if you look at the evidence that’s accumulating, all of them will produce extrapyramidal reactions. It’s simply a matter of dose. I
don’t see what is so monumentally different from what we had before. Now, what could be the effect of a weak D₂ receptor antagonist? It could reduce extrapyramidal reactions, especially when you’re comparing it with 15 mg of haloperidol. It could in turn, allow these extrapyramidal reactions to be mistaken for negative symptoms, apathy and so on. That may explain the atypicals so called superiority in treating negative symptoms, which may be more apparent than real. It could also be because some of them don’t seem to have a whole lot of sedative effects; although clozapine and olanzapine have plenty. It could account for the improved cognition, which I think is minimal anyway. So, if patients are less impaired by extrapyramidal reactions or sedation, it may contribute to social rehabilitation. But, these speculations are not proven. They’re just possibilities and I think we’re buying a lot of expense we don’t need.

TB: You are more or less saying that not only are we buying a lot, but, even with the old drugs, we are overdosing. Forget about the new drugs, because there is not sufficient evidence they are different, but are you saying that with drugs like haloperidol we should get back to the old handwriting test or something like that and use lower doses?

LH: I would be tempted to start every day on a very small dose of haloperidol and use the classic tests to determine the neuroleptic threshold. If, at that time, the psychosis hadn’t responded, using diazepam to control the behavior, then, perhaps, add a very small dose of one of the newer drugs to increase the blockade, but not crossing the neuroleptic threshold. I don’t know of anybody who’s doing this.

TB: Now, you and John Overall were among the first who tried to tease out which patients were responding to which drug.

LH: To find the right drug for the right patient has been a very frustrating experience. John and I tried it. Jim Klett and some others in the VA tried it, and we all seemed to come to no conclusion.

TB: Would it not be possible that responders remain hidden because of the measurement instruments employed?

LH: It may be that the questions you ask determine the answers you get and when you use these instruments all you are doing is codifying the mental status examination and the questions determine what areas of psychopathology you learn about. It may be that kind of clinical approach is past and we ought to think in terms of biological outcomes.

TB: Are you sure we might not benefit if we would get better clinical feedback compared to this receptor kind of thing?

LH: I wouldn’t want to knock anything clinical. I’m a hundred percent for that. You can learn a lot by talking to patients, looking at them and observing.
TB: I think you are correct when saying the questions you ask determine the answers you get. With typical antipsychotics the very first papers were not in schizophrenia. The effect moved to schizophrenia when something had to be verified in a more homogeneous population other than all psychotic patients combined. Everything is now depending on the assumption that we have a homogeneous category, a disease entity and a measuring instrument designed to show change in it. But if the disease is biologically heterogeneous and our measures are sensitive to detect efficacy in this heterogeneous population, instead of identifying the sub-population in which the drug is effective, it would be difficult to tease out that subpopulation.

LH: Yes. Of course, you have to look at it from an historical point of view. In 1955, the New York Academy of Scientists had their second meeting on reserpine, which was all on schizophrenia. They had everybody who was using the drugs, or almost everybody, including Nate and me. Not a paper in that whole bunch told what kind of psychiatric patients they were treating. Mine was the only one that tried to use the DSM-II, I think it was.

TB: It was DSM-II.

LH: My studies were blind and controlled and that captured the attention of the press. We tried to grade the improvements clinically but no instruments were used. The attention to my paper caused them to feature it on the news wire and, in a day or two every newspaper in the country had an article about the new drug for schizophrenia with me as the principal investigator. A couple of days later, the mail started in from all over the country. I’ve got a son; I’ve got a daughter; I’ve got a husband; I’ve got a wife who is schizophrenic. Nothing is helping; can I bring them to get this new treatment? It took a lot of time to answer every one of them personally, but it was impressive to see the power of the press and the anguish of people who had a relative with a catastrophic illness. Nate fully expected to go to that meeting and be the star, but I upstaged him! The Lasker award, at that time, was brand new. Mary Lasker had decided to honor her husband with the award and she was very interested to make the award for advances in the treatment of mental illness. When the award came out Heinz Lehman got one for introducing chlorpromazine.

TB: As well as Deniker and Laborit.

LH: And, Bob Noce for reerpine. Nobody had heard of Noce before and nobody’s heard of him since. He was just a State Hospital psychiatrist. I was talking to David Healy and he said, “Why didn’t you get the Lasker Award?” Then I realized I probably screwed myself out of it by upstaging Nate, because Mary Lasker listened to him. That does seem to be the only rational explanation of how Bob Noce, who was a nice simple...
minded guy, could wind up with a Lasker Award. I’m not even sure that Noce had any major publications.

TB: Let’s discuss the antidepressants. Theorizing about the antidepressants starts in the early 1960s with the discovery of Axelrod’s group that imipramine blocks norepinephrine reuptake and the demonstration of Brodie’s group that desipramine the demethylated metabolite of imipramine is responsible for imipramine’s reserpine reversal. If my recollection is correct, you had a paper on desipramine.

LH: Yes, but we never saw a whole lot of results from it, because we used too small a dose.

TB: What was the dose?

LH: Between 75 and 150 mg, and 100 mg is probably too small. I remember Brodie, who could be somewhat sarcastic; although we got along well, said if you want a drug to work, you’ve got to give it in the proper dose, and he was right. So, I never felt keen about that study; we don’t hit homeruns every time we go to the plate. Sometimes we strike out.

TB: But independent of whether the dose was adequate or not, it triggered a development which moved things from the non-selective monoamine uptake inhibitors to the selective ones.

LH: At that time, I don’t think there was much interest in trying to separate the norepinephrine depressions from the serotonin depressions. Desipramine is a selective norepinephrine blocker, but we had nothing that was selective for serotonin in those days. So, you couldn’t test the hypothesis in a clean way; although, I’m sure many people, as well as myself, thought of it. The closest I came to it was when I suggested that to some group and Sandy Glassman said he took a crack at treating depressed patients initially, with desipramine, a norepinephrine blocker, and then the failures with amitriptyline, which was the most serotonergic of the mixed drugs, to see if we could tease them out. But after they treated eight or ten patients, they all responded to desipramine, so they had no way to make the comparison and they stopped the study. I don’t even know whether they published it. There was no way until the selective serotonin uptake inhibitors came along to test the hypothesis and I don’t know anybody who did that. Do you know anybody that tested selective serotonin inhibitors vs. desipramine?

TB: There are some isolated studies. Do you think any major contribution has been made since imipramine in the antidepressant category?

LH: In my opinion, the most interesting and original antidepressant is not a serotonin uptake inhibitor, but bupropion (Wellbutrin), which, as far as we can tell, works on dopamine, but it’s not clearly defined as to how. If you look at the molecule it’s the basic phenylethylamine structure, but they
modified the side chain and this attenuated some of the amphetamine like effects. So when I see a patient and I think the depression would be ideally treated with something like amphetamine, I prescribe Wellbutrin, and it works.

TB: Would that be a particular kind of depression? In the 1964 paper with John Overall you had four different types of depression. Would one or another be more suitable for Wellbutrin?

LH: I don’t use the subtypes characterized by that rating scale. I guess I could. One thing that came out of that was the tricyclics were effective for endogenous or what we called retarded depression.

TB: Are there any other useful subtypes of depression in terms of treatment?

LH: Deniker’s group has classified a mixed anxiety depression syndrome. We called it anxious depression. We brought attention to that and it is beginning to become a very popular idea. People are beginning to think there is some sort of comorbidity or, maybe, anxiety is part of depression. I remember raising this question with a psychiatrist and he said, “I can imagine somebody being anxious and not being depressed, but I have trouble imagining somebody being depressed and not being anxious”. I thought that was not a bad summary statement. More and more, you’re getting overlaps where panic disorder, for instance, is being treated with antidepressants and sociophobia and some of the other anxiety syndromes have more overlap with clinical depression.

TB: Is there any study to compare bupropion with a norepinephrine uptake inhibitor?

LH: I think it would be interesting to compare bupropion and reboxetine.

TB: But is there any?

LH: No. Bupropion has also the advantage that it doesn’t interfere with sexual function. That’s a good selling point with Viagra being so successful. Another drug that would have been very interesting if it had lasted was nomifensin.

TB: It died because of side effects. Now bupropion is sidetracked with another indication.

LH: I don’t have any idea why it works in making people give up nicotine, but it apparently does.

TB: It looks like it does. Do you think that your argument for lack of evidence for the lack of advantages of newer antipsychotics over the old ones applies also to antidepressants?

LH: One of the earliest meta-analyses was a comparison between serotonin uptake inhibitors as a group and the tricyclics taking all the published papers where there was a comparison group was published in the British Journal of Psychiatry about 1994, and concluded, in terms of efficacy,
there was no difference. In terms of side effects, it was a trade off with a marginal advantage for the selective serotonin uptake inhibitors, but in terms of people completing treatment, there was no difference.

TB: There is another meta-analysis, a very recent one that suggests that taking into account all the different side effects the newer drugs don’t even offer advantages in that respect. They are of course differences between the side effect profiles.

LH: I’ve taken tricyclics and they’re not pleasant. I also took Prozac (fluoxetine) 20 mg a day for about ten days and if I would not have known, I would have thought I was taking nothing. I was impressed by the fact there were hardly any discernable side effects, which was much different from the tricyclics. If I had to have an antidepressant and was given a choice between a tricyclic and fluoxetine, I’d probably choose the newer one.

TB: In an advisory capacity to the State of Texas, would you suggest, if there is a major price difference, to use the newer drugs or would you say to stick with the cheapest?

LH: When the price differential is great with the antipsychotics I prefer the generic haloperidol which is dirt cheap. With antidepressants the differential is not so big. One of the things that seem to stand out is that the more disturbed you are, the more tolerant you are of side effects. Most normal people find antipsychotics to be intolerable and the same is true of antidepressants. When you’re truly depressed, the side effects are more tolerable. It may be you could justify using old drugs first and, if the patient becomes intolerant or non-responsive, switch to the newer ones. In everything in life, you have to make a judgment between cost and benefit. Since there seems to be a finite amount of money for treating psychiatric patients, I’m going to think a long time before I spend that money. When the patient says I feel a little better on one drug than I do on the other, well, that’s tough. You’re getting well. That’s what counts. In the case of a local situation, if schizophrenic patients are admitted to the mental health authority and treated with the new drugs, there wouldn’t be any budget left; nothing for lodging, nothing for social rehabilitation, nothing for vocational assistance, all of the other services that patients need in order to function in life and stay out of the hospital. So, if you’re buying expensive drugs and have to give up all the rest of the treatment, that’s a bad bargain. We have to view the situation broadly. Nobody thinks that drugs, alone, are going answer the problem. The best we can do is make it possible to use other avenues to try to improve the lot of the patients, and if you can do that by allowing them to live or function in the community and do some sort of productive job, those are the outcomes by which we measure success. We don’t have a lot of people who have
been schizophrenic go back to being concert pianists. They may try, but it seldom works. So, you have to set your sights as you would for any handicapped person, because if they have a physical handicap, you try to teach the patient how to work around it and do the best they can with the handicap. You don’t think you’re going to get rid of it, but you’re going to try to work around it and I think we have to do that with our impaired psychiatric patients.

TB: I think you have become interested at a certain point of time in the cholinergic hypothesis of Alzheimer’s disease and we didn’t talk about that as yet.

LH: We didn’t have anything to do with the development of it. It came from Peter Whitehouse and his colleagues where they traced these cholinergic tracks in the brain and showed there was some relationship between them and Alzheimer’s. There was indirect evidence suggesting a cholinergic hypothesis and I and Kenneth Davis, got very interested in this. I had run across an abstract in Federation Proceedings by the guy at MIT who worked with Axelrod, in which they indicated you could use choline as a precursor for acetylcholine in the brain. Again, we flooded the whole brain. It turned out not to be very practical, because when we started using it on patients the ward smelled like an old fish market; the choline changed to trimethylamine and that is what makes dead fish smell. We tried to deal with that, but had the impression we were losing the nursing staff, so we stopped it. Lecithin has to be metabolized in the body to free choline and it made much more sense.

We also tried physostigmine and replicated studies Dave Janowsky had done with in mental patients and that, too, caused a rather dramatic change. One of our manic patients, as we were doing the physostigmine infusion, suddenly became very depressed, starting to cry, felt awful and we had to stop. That was a rather dramatic change of mood which suggested acetylcholine might play a role in the switch process, which has never been fully elucidated. Most people think it’s due to dopamine. In tardive dyskinesia, with the physostigmine infusion, we could show by videotaping them and blind ratings there were substantial changes in abnormal movements but they are extremely difficult to show because they’re so variable anyway.

TB: Anything else you like to say about drugs in Alzheimer’s? Did you work with any of the nootropics?

LH: No, but as I said it before I was first with Metrazol and Hydergine.
TB: What would you think was your most important contribution to psychopharmacology?
LH: I feel somewhat disappointed I can’t point to a single real discovery in the sense of something vastly new or revolutionary. I attribute it partly to the freedom I’ve been given to follow wherever I want to go, which tends to make you more diffuse compared to somebody who says I’m going to focus on one thing and find the answer. If I had it to do over again, I’d be more focused.

TB: But you contributed a lot by trying to establish where we really are and constantly reviewing the whole field. You did that with great regularity.

LH: Yes, I think one of the contributions you can make is to try to reduce data into something understandable and coherent. I had a good ability to do that. As far as the experimental contributions are concerned, I would say the most important, probably, was the introduction of controlled clinical trials in psychiatry. It would have happened without me, but I think I gave it a little push.

TB: A start.

LH: The second thing might have been the ability to look at drugs beyond their psychiatric effects, to study including the complications of the use which I don’t think a whole lot of people in the field were able to do.

TB: You wrote several books and some of them had several editions. I think one of them is just getting into the fourth edition, right?

LH: Clinical Pharmacology and Psychotherapeutics. It had just three editions.

TB: Was the book translated into any other languages?

LH: No, the publishing house doesn’t seem to have much zip.

TB: The book which is translated into many languages is the one with Ole Rafaelsen.

LH: Yes, Ole and I never made a penny off that book, but that wasn’t the goal and it served the purpose Ole had in mind. Ole was a truly remarkable person. I remember the first time I met him, I said, “Come on over to the hospital” and he replied, “I’d like to see what’s going on in the research area”. So, at that time, I was Associate Chief of Staff for Research and knew all the research going on so I took him everywhere, neurology, cardiology, psychiatry and surgery. Within one minute, he could be talking intelligently to the person describing their research. I never ran into anyone who had such a broad based knowledge of medicine as Ole. He knew what was going on.

TB: He was involved in research in diabetes, right?

LH: Yes, I visited his outfit in Copenhagen and he had several things going, but some of them were not psychiatric. He, also, had been trained in medicine first; although he did have some formal training in psychiatry, which I never bothered to get. I had the utmost respect for him and he was a delightful person. One of his unknown accomplishments was a
book of erotic limericks of his own composition. He was just a wonderful person.

TB: We have a few more minutes and it might be something you would like to talk about.

LH: Some time ago the former president of the CINP had some say whom he wold like to see to follows him. The first person I wanted was Arvid Carlsson and we got him. The next person I wanted was my other idol, Paul Janssen and we also got him. Finally I got Ole, after Paul Kielhotz and Biff Bunney. It was only two or three years after his Presidency that he had the tragic accident that killed him. If he had lived he would have been a big figure.

TB: Leo, thank you very much. I think we used up our time. I really appreciate your contributions and the infomation you shared with us. It was very enjoyable to listening to you.

LH: Well, you’ve been enjoyable, too.
Interviewed by Andrea Tone
San Juan, Puerto Rico, December 12, 2004

AT: My name is Dr. Andrea Tone and we are at the ACNP Annual Meeting in San Juan. It is December 2004 and I’m interviewing Dr. Turan Itil. I wanted to start with some basic questions about how you got interested in medicine in Turkey and what the state of the field was at the time you entered the medical profession?

TI: I originally wanted to be an engineer, but I could not pass the entrance examination for the school in spite of being an honor student in high school. I could enter medical school without any examination.

AT: It was easier, at that time in Turkey, to get into medicine?

TI: Exactly. I went to medical school with the understanding I would go back a year later to engineering. But in that year my father died so I stayed in medical school.

AT: What interested you among the different specialties?

TI: I was always much more interested in the scientific aspects of medicine.

AT: Did you know when you entered medical school that you would focus on neurology and psychiatry?

TI: No, when I finished medical school I wanted to be a surgeon. But that was not possible in Turkey.

AT: Why?

TI: We didn’t have a neurosurgery department in 1949.

AT: So, you picked psychiatry as a second choice. Why?

TI: I was accepted in neurology and psychiatry at the University of Tübingen. The professor was Emil Kretschmer whose name I knew. I had read two of his books, one on Medical Psychology, and the other on Body Type and Character, and I liked both very much.

AT: That’s an interesting way to get into the field. What was “in vogue” in psychiatry at the time?

TI: Psychiatry was very much influenced by Freud. Binswanger was also influential. But Kretschmer was the father of biological psychiatry.

AT: Tell me about your first experiences in psychiatry at Tübingen?

TI: At the time I arrived in Tübingen the hospital had a big floor with lots of bath tubs, and patients caught up by nets treated by sitting in warm water in the tubs. People were screaming and crying and the best treatment for that was thought to be cold water up to the neck. They were also given barbiturates so they either slept or were awake screaming and yelling. Then, suddenly, chemical treatments arrived and the wards changed; the doors were opened.
AT: You’ve been doing work with electroencephalography for a long time. Tell us how you got interested in that. Did it have anything to do with your desire to be an electrical engineer?

TI: Maybe, but only in part. I moved from the University of Tübingen to the University of Erlangen in Germany, and we used to get lots of patients with phantom pain.

AT: Were these amputees from the war?

TI: There were lots of amputees from the war but also others. The French published a paper at the time which suggested that a new drug, promethazine, could relieve phantom pain. My professor, whose name was Fleischgel, said we should study this new drug in our patients. In some patients it worked whereas in others it did not, and I couldn’t understand why. One of my professors said it could be because in some patients promethazine didn’t get to the brain. That made sense so I asked how to find out. First I was told you can’t do that but then, the professor’s chief assistant told me, “Somebody in the twenties wrote a publication that the electroencephalogram shows whether a chemical has an effect on the brain or not”. So, I looked and there were lots of publications in German. I was very impressed and could not understand why people didn’t use electroencephalography for that purpose. I went to our EEG department and was told you can’t show whether the drug goes to the brain or not. They didn’t believe in Hans Berger’s findings. So, I learned how to do and evaluate an EEG and saw the effects of the drug myself. I started to do more and more and around 1957, I took all my EEG records and went from one professor to the next, asking for advice how to proceed. I was told that in order to be scientifically acceptable my findings needed to be replicable and to show predictability. Others told me if I quantified the EEG it would render my findings replicable and predictable. So I didn’t know what to do.

AT: I see. What happened next?

TI: In 1958, at the first CINP meeting in Rome, I gave a talk and Max Fink gave a paper in the same symposium. We were both tremendously enthusiastic, because both of us reported the same effects of chlorpromazine on the EEG. This united us and we became friends. He said, “We will start quantitative EEG studies in the United States; come and we will do it together”. Professorship in Europe is not awarded as in America. You have to pass lots of examinations, write a thesis and do all kinds of other things, and I was in the middle of all that. So I said, “I would like to come, but I can’t right now”. It took me five years to get to the United States but once I finished my examinations I came. When I first asked my professor for a one year sabbatical to work with Max he was at Hillside Hospital on
Long Island. But, at the beginning of 1962, he wrote to say he’d moved to St. Louis to be in charge of a Research Institute with a computer and all the new technology. So, in 1964, I went to Missouri for one year and that one year extended to many more.

AT: Max is very persuasive!
TI: Very persuasive, but I wanted to go anyhow, that was the goal.

AT: Let me ask you something. There’s a lot of emphasis on MRI scans and how you can look at the brain of someone with schizophrenia and recognize it is completely different from a normal patient. One of Max’s pet peeves is that this kind of brain mapping is being celebrated as brand new but he talks about the work the two of you did and the central importance of the electroencephalogram as a technique that was going on decades earlier. Why has this technology that you pioneered fallen by the wayside while brain imaging via MRI’s seems to be sexy and is being presented as brand new, when what you were doing was revolutionary?

TI: As a Harvard professor put it, some of the new technologies have advantages to the old ones. The electroencephalogram was discovered in 1920, long before computers, by a psychiatrist who didn’t understand technology. You know why he discovered the EEG?

AT: No.
TI: In his biography, he wrote that he had one daughter and one son. The son went from Magdeburg to Duisburg with his friends and a couple of days later his daughter came to see him at the hospital. He thought, that’s very unusual, because his daughter never come to the hospital. She asked, “Did you hear from my brother”? When Berger answered, “No, why”? she said, “Please send this cablegram, something’s happened to him.” So, Berger asked, “What is it”? And she replied, “I have a feeling something happened to him”. The father sent the cablegram and the son responded, “Everything’s alright”. When the son came home he asked his father, “Why did you send this cablegram? It’s unusual”. The father told him, “Because your sister asked me”. The son said, “She was right. I was with friends on a winding road and, suddenly, we heard a horrible noise and saw a big water vehicle with horses and carts coming towards us and we were scared. But how in the world did your sister have this kind of feeling”. Then, Berger writes, “I always thought that the brain may produce some electrical activity, that it has a certain kind of synchronized activity. My daughter and son, because of their love for each other, synchronized their brain activity. Because Berger thought electrical activity travelled through the air he discovered the electroencephalogram. That kind of discovery seems absolutely crazy. What neuroscientist would accept this sort of reasoning?
AT: But so much of the history of science and technology comes about in this way.

TI: Yes, but many of them aren’t accepted. What Dr. Berger wrote, nobody remembers any more; what people do remember is that he found when patients have epileptic seizures, they have atypical brain waves. Even today, we don’t have of any other method to determine this. So the EEG is good for epilepsy. It’s true that the EEG once in a while shows a brain tumor, but it is not a good method for detecting brain tumors. It is a method for detection of physiological changes. What Berger was really interested in was the relationship between the changes in electrical activity and what is going on in the mind. The detection of epileptic activity was a by-product. He didn’t care so much about detection and localization of tumors. He was interested in what goes on in the brain of patients with schizophrenia. He saw the effects of mescaline, barbiturates, and cocaine. His interests were more in relating changes in electrical activity to the soul and not to tumors. Because, at that time, the only tool for neurologists to determine substantial change in brain was the EEG it became a method for tumor detection. And for that it did not fulfill expectations. The angiogram and the pneumoencephalogram were much better, even before the CAT scan and MRI were introduced. So neurologists didn’t like it when Max and I computerized the electroencephalograph, and developed quantitative EEG; it was not a tool to diagnose tumor but to describe cerebral process. It’s a functional tool. Another problem was that no major company became interested in our computerized EEG.

AT: I see the problems you encountered.

TI: Another problem is that, after all these years, we still don’t know what is behind the electrical waves. What is the scientific basis to the chemical process of the brain, the relationship between electrical processes to changes in the dopaminergic or adrenergic system, etc? Fortunately we could relate the electrical changes to behavior.

AT: Before you and Max developed quantitative EEG you studied the effect of several drugs. Could you tell us something about your early research?

TI: I mentioned already my interest in promethazine. I wanted to know why some patients with phantom pain improved and others did not. Then, as I mentioned, I studied chlorpromazine. I was a Turkish citizen and I couldn’t get a salaried job in Germany, so Bayer gave a stipend to the University and I was paid from that to study EEG changes with compounds they developed. The goal was to find another chlorpromazine-like substance on which patients would not be slowed down and sedated. We screened dozens of compounds and eventually found one that was more powerful than chlorpromazine. It was butaperazine, eventually marketed in Europe.
AT: Was it marketed in America?
TI: No, because it also produced more side effects. In this country, everybody is more conscious about side effects than in Europe. After I moved to the United States we started computerized quantifications of the EEG and when Max and I started to publish the drug companies became interested and asked whether we could differentiate between antipsychotics, antidepressants and anxiolytics. I discovered the antidepressant effect of mianserin by quantitative EEG.

AT: How did that happen?
TI: Organon went to Max who was by that time in New York with a potential psychototropic substance and Max sent them to me in Missouri. I found it showed a similar profile to amitriptyline. To celebrate the discovery Max gave a party at his house in Long Island and invited me from St. Louis. At the party there was a lady, Mrs. Summer, an intellectual property lawyer. Max introduced us and suggested I tell her the mianserin story. She convinced me that I could obtain a patent for the drug. In the meantime, the Organon people asked me to go to Europe and I went with Marty Katz, who was a big shot at that time at NIMH. The first time I met the pharmaceutical company boss, he asked, “Do you really think mianserin has antidepressant effects”. I said, “I think so” but in the meantime, I gave the drug to a former professor of mine in Turkey who gave it to 10 or 15 patients and thought it was a very good drug because it didn’t produce dry mouth and constipation and was effective without the side effects of tricyclics. At another clinic the drug was given to 25 or 30 patients and it looked like it had antidepressant effects. I showed these findings to the boss at Organon who recognized I had discovered the antidepressant effect of mianserin, and asked “What do you want”? I replied, “I just want appreciation, that’s all”. That was the first time in history that the antidepressant property of a drug was discovered by quantitative EEG.

AT: You were trained in Europe and started psychopharmacology there. What were the key differences between psychopharmacology there and here at the time you arrived in America?
TI: In Europe we were much more interested in psychopathology. Psychopharmacology started in Europe, and was relatively late coming to the United States where it entered a heavily analytically oriented environment in practice and academia. Even in Europe, if you were a psychopharmacologist, you couldn’t get a Chair in Psychiatry in the 1960’s. In Germany there were nineteen Chairs, but only my Chairman, Professor Flügel, was involved in neuropsychopharmacology. In Europe I used to put on my white coat when I saw patients and when I did that in Missouri the nurses complained that one should not upset the patients.
AT: By wearing a white coat?
TI: By wearing a white coat. Gradually, in the middle of sixties, changes began. It is fantastic what has occurred in the last twenty years, in neuroscience. But at the clinical level, I think we neglected our job. For example we give too high doses of medication. I started three of my patients on ten milligrams of amitriptyline twice a day. No doctor trained in America will give ten milligrams.
AT: That’s a very small dose.
TI: A very small dose. I have an obsessive compulsive patient who gets stimulated and becomes very nervous even given just one dose of fluvoxamine (Luvox). Medications should be titrated, starting with a low dose. There are all kinds of publications that it takes three weeks before the onset of antidepressant effects. That’s not true. We see the effects of an antidepressant on the brain, within three hours, very significant effects and cumulative effects within a week. Marty Katz and his group have done beautiful studies showing this. I don’t know whether you read their studies showing effects start in one week. That has a significant impact on the economy of treatment. Any patient that receives an antidepressant will tell you they are affected within three days. As a matter of fact, if the drug doesn’t have some effect by the second or third day it probably will not help. I have worked for fifteen years with treatment resistant schizophrenic patients and we realized that after long term treatment with neuroleptics their EEG patterns have changed. We don’t know what this pattern change means but we know that these patients become resistant to neuroleptics. We know that this has changed and possibly their receptors are blocked and don’t respond. If such patients are given five thousand milligrams of chlorpromazine it’s a complete waste of money.

AT: Leo Hollister said, before he died, that one of the problems in psychiatry is that you have people suffering from schizophrenia or depression and the drugs we have today are no better in dealing with illnesses than they were at the time psychopharmacology began. It seems that one of the things you’re suggesting is that it’s not necessarily that the drugs don’t work, but we don’t administer them properly?
TI: Exactly. I agree, partly, with Leo, but I believe even more that we don’t do a good job. We shouldn’t be satisfied, because none of the antipsychotics cure the illness. With antidepressants there is some improvement but not enough. They have a wonderful effect, a stimulant effect, a well being effect, almost like cocaine, but depression is still there. All of the antianxiety drugs produce, eventually, addiction if you look carefully. My best story is a patient taking an antidepressant with pretty good effects but not
good enough, and I asked, “What do you need”? He replied “I don’t have money, and whatever you do I want to improve”. So, I said, “Why don’t you go to the gym and exercise till you are physically exhausted”? Six months later, he wrote me a letter and said, “My uncle in Oklahoma has an old mine so I went there and started to work, physically, as you said. I did this every day, and got exhausted until I hit silver. Now I’m, making money, I’m happy and I don’t need any chemical”.

AT: How come when we go to conferences we don’t hear that? I think I know the answer, but I want to hear what you have to say. We go to conferences like the ACNP and the CINP but in line of these conferences are panels devoted to a drug vs. the treadmill. It’s all about this pill, that pill and another pill.

TI: Because these meetings don’t even accept clinicians any longer. You have to make a significant scientific contribution to get accepted.

AT: Is that true? I didn’t know that.

TI: People, to be accepted, have to have publications and a reputation and how can a clinician in the battlefield get the necessary reputation? They say those who don’t have it should be with the American Psychiatric Association, the Psychological Association, etc. I disagree with that.

AT: I interviewed Malcolm Lader in Paris this summer and he said one of the problems with the way programs at scientific meetings get structured is that people only attend if their way is completely paid. They usually got the money from one or another drug company. If they participate in the program usually, that person will be encouraged to mention some of the drugs these companies produce. Malcolm’s point is that, there’s no true intellectual integrity, where the truth can surface, if everyone talking science is in the pockets of the pharmaceutical industry.

TI: The ACNP was the most resistant society to the impact of the pharmacological industry.

AT: The most resistant?

TI: Until ten or fifteen years ago. It went for thirty or forty years without too much influence by outside forces. In the last ten or fifteen years, unfortunately, that’s not the case any longer. Once they dissolved the Psychopharmacology Branch of the NIMH many people didn’t get grants and became dependent on somebody outside the government to pay. When the Early Clinical Drug Evaluation (ECDEU) program was dissolved investigators became dependent completely on drug companies.

AT: Do you think patients are adversely affected?

TI: Not because of changes in the society.

AT: Looking back at your career what would you say have been the key contributions you’ve made?
TI: The detection of the effect of oral psychotropic drugs on the brain and the identification of differential profiles of drugs with different clinical effects such as antipsychotic or antidepressant. I discovered antidepressant properties of three drugs and patented them. First, I discovered the antidepressant effects of mianserin, as I told you. Then, I showed that the EEG effects of mesterolone, a synthetic androgen preparation, are similar to imipramine. We have done a big double blind study in a depressed population and shown that, indeed, it’s an antidepressant. A German company was very enthusiastic about it but since testosterone may produce prostate cancer the substance was not pursued further. In females it is known that estrogen helps menopausal depression and I showed that the conjugated estrogen, estradiol valerate, produces similar effects on the brain as antidepressants.

AT: Do you think there will be a market for those things? I see testosterone patches and gels being advertised to men at doctor’s office in the United States for loss of libido?

TI: Gradually, it’s coming. It will be marketed after my patent expires. The fact that brain electrical activity produces such information is probably the most important contribution, which is not accepted.

AT: So, those are your contributions, discovering the drugs and the fact we have this technique to monitor the functioning of the brain.

TI: What I have also found, but haven’t published yet, is that with a certain type of quantification of the electroencephalogram, we can show a significant difference between Alzheimer’s patients and age-matched controls. We are initiating that as part of a diagnostic procedure. When we are young, in general and on average, we have sixty percent of activity in our brain in the occipital area, and then by the time we are sixty that declines to forty percent. When we are sixty or above and also demented, that declines to twenty percent. And, when we have advanced Alzheimer’s, it declines to ten or even five percent. That’s a significant decline due to age and dementia. Every effective cognitive activator with an effect in Alzheimer’s, produces an increase of occipital-β, so it reverses the decline. That kind of reversal I also discovered in schizophrenia with effective antipsychotic drugs. Every effective drug decreases the fast-β-activity in the EEG.

AT: That’s really interesting. What do you think of ECT?

TI: I think ECT is a wonderful, very effective treatment in certain patients and certain conditions, like certain catatonic stupors and some depressed patients. The problem that my friend Max Fink would never accept is that we don’t know what happens in the brain when we give ECT.

AT: We don’t know?
TI: We don’t and clinicians don’t want to know. They should do, at least, an EEG and memory tests before and after ECT, but they don’t. There are many publications that memory declines and there are psychological, behavioral and certainly cognitive changes.

AT: In your bibliography you have an article, Looking at the Electrical Activity of Lobotomized Brain and Non-Lobotomized Brain.

TI: Lobotomy was wonderful for certain types of patient. Aggressive patients who were killing people and could not be controlled by any means were not aggressive after lobotomy and became a different person. My brother had a very aggressive cat and one day a car hit the cat. The cat survived and now it is completely tame. So, lobotomy is wonderful for certain types of patients and you need to realize the consequences. Do you know that now in our hospitals chronic schizophrenic patients probably have the equivalent of a lobotomy?

AT: I didn’t know that. How is that so?

TI: By using high dosages of medication.

AT: I see. Max Fink and I have talked about people who resist ECT because it seems like a much more invasive violent procedure than prescribing drugs, which we think of as very benign, like taking a vitamin. It’s almost as if we’re programmed not to think about the impact of ECT and of these drugs on the brain. It’s a huge cultural problem.

TI: The fact remains that we have very invasive procedures which give good results, but without knowing what will happen in the years to come. There is the famous saying, father had a very successful operation, but, now, he doesn’t look like my father.

AT: Why do you think proponents of ECT are reluctant to figure out what’s happening to the brain? You are saying they don’t want to know because they’re scared to find out.

TI: Sure, the same thing is happening with anesthesiologists. We tried to convince anesthesiologists to take quantitative EEG measurements because there is a possibility of damage that can be reversed. The brain should be examined before anesthesia. I had a very simple operation, but just before the anesthesia, I said to the doctor, “You checked everything in my body, but not my brain”. He was shocked and asked, “What do you mean? We did a physical and a neurological exam”. I replied, “I know you did the neurological examination, but you really didn’t check out my brain”. He was shocked and angry.

AT: How expensive is it to do an EEG?

TI: You can have a twenty-five dollar EEG.

AT: So, there’s really no excuse not to use it, except that it takes extra time.
TI: And that people would say let me find out first what those findings with the EEG mean.

AT: Right.

TI: The same happened when the electron microscope was invented; people asked why spend so much money to see much smaller objects than bacteria. Why do we need to see more? The answer is you want to see more, because eventually we will find something.

AT: So you think that if people keep doing it, it will eventually tell us something. When your students do these studies, what do they find?

TI: We are trying to use quantitative EEG for early detection of psychiatric disease because by the time you can use an MRI is too late. If there is already atrophy you will not be able to treat it effectively. We still have the problem of saying what a normal brain is. We get norms by analyzing our database but the spectrum is wide. The best solution to overcome this problem is to have information on the brain from early on, as we have on the heart. You do check-ups from year to year and it’s very cheap in the sense that if you treat those illnesses early, you have much more success than if you treat them later.

AT: Let me ask you a couple more questions to fill in some of the information we have not covered. Who have your key mentors been?

TI: I made a big mistake, I didn’t have a mentor. When I moved from Erlangen to St.Louis I was too old to have Max as a mentor and he was more involved with administration than the laboratory. In Germany I published many papers with somebody named Bente and he was the first author because his name began with B. Unfortunately, I didn’t have a reputable mentor and I think Max probably had the same problem.

AT: He did.

TI: What we were trying to do was far ahead of our time. I think it still is.

AT: Do you have any regrets about the way your career developed?

TI: I’m really happy. I’m lucky I wasn’t killed because I deviated from the norm.

AT: Metaphorically, of course! Where do you see the profession headed? What do you think it’s going to be like fifty years from now?

TI: I think neuroscience will make it possible to understand things better by finding a pattern for certain psychiatric illnesses. If you have drugs, of which one has anticholinergic, another serotonergic and a third, noradrenergic activity but all show the same pattern on brain electrical activity, those biochemical differences have nothing to do with the effect of the drug on depression. When you live as long as I have, you know that every ten years we have another hypothesis for depression. In my lifetime, we had four different hypotheses and, obviously, none of them is true. Every
one of them had a little bit of truth. Placebo is a wonderful drug; it has an effect in psychosis in about thirty percent of patients, in anxiety, fifty percent, and in depression, forty percent. It’s a wonderful drug. We don’t know the real cause of any psychiatric illness and therefore we don’t have a real treatment for any of them. Neuroscience will eventually help to find the cause. Fifty years or, hopefully, thirty years from now, neuroscience will have found something. In the meantime patients still need the kinds of treatments, psychological and pharmacological that we have.

AT: Can you think of anything else you would like to add?
TI: I’m setting up Alzheimer’s centers for early diagnosis in the underprivileged population. These are people who don’t have a job and don’t work. They don’t have relatives or friends to bring them to the doctor. In Harlem, we have the beginning of an epidemic of Alzheimer’s.

AT: That’s interesting.
TI: It’s very difficult because nobody cares and the system discourages you from offering those people better health. You cannot send a car to bring them to the center, because that is, according to Medicare, illegal. But, if you don’t do it, nobody comes. In thirty to forty years we will have ten to fifteen million people who will need twenty-four hour a day care. That’s a big, big problem. So, that’s why I’m starting these centers now.

AT: Any other work you want to mention?
TI: We studied the children of schizophrenic parents in Denmark. Mednick and Schulsinger started the study and I was involved with the electrophysiological part. We published two articles in the American Psychiatric Association Journal, suggesting that a certain group of children would become schizophrenic; we predicted it in a sealed envelope. That study was supported by NIMH and WHO. I have also done the largest study on terrorists.

AT: Really, what did that involve?
TI: It involved 2,500 terrorists who were caught and convicted, because they either killed somebody or were at a killing scene.

AT: What did you find out?
TI: They were not compulsive, they were not neurotic and they were not sexually disturbed. They were normal, but had very low intelligence, far lower than the control population. Those killers were specifically profiled by the leadership of Turkey. They were nice kids, not too smart and not uncontrolled. They obtained marijuana first and then a gun. My results helped to control terrorism in Turkey.

AT: That’s great. You must have saved lots of innocent people. Maybe you’re not allowed to say this, but have you been approached by federal authorities in the United States to profile terrorists here?
TI: I’ve been approached, many times. But to finish the story in Turkey; I had an office in the research center there and a terrorist’s bomb killed almost everybody there. They were looking for me and couldn’t find me, but still they bombed the center.

AT: Did you worry about your safety after that?
TI: Absolutely!

AT: I don’t think I’d sleep again if that happened to me. Is there anything else you would like to add?
TI: I would like to say that the best drugs were discovered in psychiatry by accident and that looking at the effect of a substance on the electrical activity of the brain is the simplest method for identifying the potential therapeutic profile of a drug. We now have some data which indicate that the doses in which psychotropic drugs are used are counter-productive for achieving therapeutic effects.

AT: How long will it take to get those data published?
TI: Another ten years.

AT: I would like to interview you again in ten years time. Thank you very much. I really enjoyed this.
TI: I enjoyed it too. I’m free now, right?
AT: You sound like you’re in the electric chair! You’re free!
TI: Fantastic, then I can go.
This is an interview with David Janowsky for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College. It is December 10, 1997. I'm Burt Angrist. You have done pioneering work in schizophrenia and other areas. How did you get into this field?

I was in medical school and planning to be a pediatrician, but they had psychiatry rotations in the third year and I liked them. They had us go to the county hospital, observe patients and write them up. There was an amphetamine addict who was very psychotic, and I became fascinated by him. It seemed like surrealistic existential literature. So, after I started a pediatric internship and found it too sad and boring, I decided I would go into psychiatry even though, in medical school, it was a pariah specialty. In terms of the psychobiologic field, I fell into that by accident. My original goal was to be a milieu therapist and run a therapeutic community. However, as a first year resident, I had a patient with very severe pre-menstrual tension. In retrospect, she also had a borderline personality disorder. She became agitated, aggressive, and suicidal around the time of her periods. I became interested and with my first year residency attending, Rob Gorney, I worked out a project where we collected urine, looking at ovarian hormones and mineralocorticoids over the patient's menstrual cycle. I had a hypothesis the mineralocorticoids would be increased during these episodes, which they were. So, that's how I got into the psychobiologic field. Around 1965 or 1966, I had to make some choices. I could become a child psychiatrist, ultimately enter the military in the Berry plan and possibly go to Vietnam, or try to go to the NIMH Public Health Service. This choice got you out of the draft and was, essentially, the same as being in the Coast Guard. So, I decided to give up Child Psychiatry and applied to NIMH to be a Clinical Associate at the Clinical Research Center in Bethesda. We called ourselves the Yellow Berets. I was supposed to work with Jack Durrell, a famous psychiatrist at the time. I was to run a therapeutic community and somebody else was going to run a regular ward, to compare outcomes and see if therapeutic communities really worked. At that point, I was a very "left-wing" type of guy. It was the sixties and the drug revolution was beginning. Somehow or other they cancelled the project and assigned me to work with William Bunney, a psychobiologist, working with corticoids and depression. As a first year Clinical Associate they had me run the research ward. Naturally,
I tried to turn it into a therapeutic community, much to Dr. Bunney’s consternation. By the second year I did some research on manic interpersonal interactions which led to my Playing the Manic Game paper, probably my best work ever. I also performed psychobiologic research on ovarian hormones, catecholamine and serotonin interactions with John Davis, who was a year or so ahead of me at NIMH.

BA: He was there?

DJ: Yes, a lot of people were there who became famous: Will Carpenter, Dennis Murphy, Fred Goodwin, John Davis, Herb Meltzer, David Kupfer, Richard Wyatt, and Keith Brodie were all Clinical Associates. I was a rebel at that time with the community therapy idea. Similarly I wanted to study premenstrual tension but Bunney wanted me to study catecholamines in depression, saying this was a hot area. So, I did work with progesterone and estrogen, looking at synaptosomes and the release of norepinephrine, serotonin and dopamine when exposed to ovarian hormones. I passed on doing clinical work with catecholamines and depression and that was probably wrong since the area became very popular as the years went on. Nevertheless, I had fun doing premenstrual tension research and felt it was my own thing. So, that’s how I got started; it was serendipity that I ended up in Bunney’s group.

BA: I first encountered your research when you were working with John Davis in Nashville. How did the transition go from NIMH to Nashville?

DJ: After two years my time at NIMH was to end. No surprise to me, nobody asked me to stay. I interviewed at Stanford and was rejected. I was then interviewed at the University of California and invited to be a faculty member. So I went to work at Harbor General Hospital, part of UCLA, setting up a crisis emergency service. There was supposed to be an inpatient unit but it was never built; instead I set up an outpatient crisis emergency service in 1969, doing no research at all. About two-thirds through the year, John Davis called up from NIMH and said, “I’m moving to Nashville, to Vanderbilt and Central State Hospital, where we’re setting up a research ward. Would you like to come and help me do it”? I was enjoying my clinical work, but my wife didn’t like LA.; there was too much smog and congestion, so Nashville sounded intriguing. In 1970, we moved there and John Davis, Ed Fann and I set up a research ward at Central State Hospital. I was the research clinician who ran the ward and John was the brains behind the outfit. We did psychobiologic research and John was my mentor, and an excellent one at that.

BA: What kind of projects did you do?

DJ: We did a lot of projects, some of which died and others went very well. The one that was most fortuitous for me was one based on John’s idea
that he could turn off tricyclic antidepressant and antipsychotic induced confusional states, which he thought were cholinergic, with physostigmine. Once we had physostigmine I began to read about how the heart was regulated by parasympathetic and sympathetic nerves and thought this might be a parallel to mania and depression in the brain. So, we gave physostigmine, which blocks acetylcholine breakdown, to manic patients and the mania went away and some became depressed. Then we gave it to depressed patients and others who had recovered from depression and they became more depressed. So we thought we had a model depression syndrome. That work has progressed over the years in many different directions and led to the adrenergic-cholinergic balance hypothesis. Another experiment, which came primarily from John Davis, involved the dopamine hypothesis of schizophrenia, and we began to think about giving, methylphenidate (Ritalin), to psychotic patients to see if it would increase their psychotic symptoms. A lot of this work was based on yours and of John Griffith’s. We found that we could activate psychosis in patients, and differently from what you were saying, they could be on dopamine blocking antipsychotics and methylphenidate would still activate them. Once the drug cleared the body, the increased psychotic symptoms went away. We decided we could use this as a diagnostic test for people we suspected of being psychotic, who weren’t talking very much. We were also looking at our finding from the perspective of what methylphenidate does to transmitters.

BA: The mechanism of action?
DJ: Yes. So those were the highlights of my work in Nashville. It went on for three years until 1973, when John Davis moved to Chicago to become leader of research at the Illinois State Psychiatric Institute. John asked me to join him, but again my family didn’t want to go into a cold climate and I didn’t either. I had an opportunity to return to San Diego, my home-town, to be a faculty member at UCSD. So, in 1973, we moved and I did research, ran a ward and a consultation-liaison service. In 1978, the Psychiatry Department at UCSD put in for an NIMH sponsored Mental Health Clinical Research Center (MHCRC). The Chairman was Lew Judd and Arnold Mandel was the Ex-Chairman and the department’s most famous researcher. They asked me if I would be the head of the Center if we got the grant and we did.

BA: By then you had considerable reputation. The cholinergic-adrenergic imbalance and methylphenidate challenge had got to be very well known by that time.

DJ: At that moment, in that department, I might have been the only one doing psychobiologically oriented research, or even thinking about it. So we
set up the MHCRC and it was a very fruitful time. I primarily pursued the directions I’d started before. I did some methylphenidate work looking at projective tests and what happens when you give methylphenidate to normal subjects and schizophrenic patients. I worked with Craig Risch and, under my mentorship, he looked at neurohormones and the differential sensitivity of increasing β-endorphin and ACTH after cholinergic challenges in depressed patients. We confirmed we could activate depression in depressives with physostigmine. We looked at the effect of marijuana on simulated flying test, and on therapy, as well as whether methylphenidate could reverse the perception of uncaring by a therapist or significant other in depressed patients. Another study involved rapid tranquilization with haloperidol, using high doses vs. low doses. We showed that the high compared to the low or medium doses didn’t make any difference to effectiveness.

BA: That was one of the first studies to show that.

DJ: I think that was one of the first studies to show that medium doses of haloperidol were as good as high doses. When you run a Center a lot of projects get done. It was about 1984 that Chris Gillin came to San Diego from the NIMH. That led to a series of studies he’d started in Bethesda, looking at cholinergic supersensitivity in depression by evaluating shortening of REM latencies, a sleep parameter. It was fun to have him to collaborate with. We also started a psychopharmacology and psychobiology training program at San Diego, which produced a number of people who have gone into academia.

BA: Who are some of the people?

DJ: Jeff Rausch is one. He is now vice chairman at Augusta, Georgia. Craig Risch, who is at Charleston, is another. Mark Rappaport was also a mentee as were John Kelso and Bill Byerley.

BA: They were all your students?

DJ: The Center was the heart of their Fellowship. It wasn’t like places where you get farmed out to somebody specific. They were involved with running the ward and they did projects, with me, Chris Gillin, or sometimes Dan Kripke, who did light and rhythm research, which I was also involved in.

BA: It sounds like it must have been a very vital atmosphere.

DJ: I think it was very lively, active and facilitative. It was very nice and it was in the VA, which had advantages. We could get VA money as well as the NIMH Center money for different things. One of the directions was the naloxone - schizophrenia idea. This went nowhere following much hoopla by others and we bailed out.
BA: I should have asked at the beginning how you get interested in psychopharmacology in the first place?

DJ: Although I had a very strong psychotherapeutic-community perspective, I was aware that the drugs I was using as a resident in the mid-1960s were very effective. Training was so psychoanalytic and psychodynamically based in my residency that you’d use drugs, but you wouldn’t talk about them. You would talk to your attending about it, but in a conference, that wasn’t where the focus would be. I felt that drugs could be a tool for understanding the brain, and that was a whole new area that was wide open. I went into psychiatry, in part, because psychopharmacology was a new frontier.

BA: You saw it as a tool and a source of insight?

DJ: I saw it as a tool for research. People knew a lot about drugs to treat diabetes but psychiatry was a wide-open field.

BA: What was the first work you presented and where?

DJ: I think it was in New York City. It might have been about 1970, or maybe 1971.

BA: Was it about methylphenidate?

DJ: It was the methylphenidate work in schizophrenia, and it was at the American Psychopathologic Association annual meeting. John Davis arranged for me to present our data.

BA: That was your first presentation?

DJ: Yes, where I formally presented something at a meeting.

BA: I have some questions you can address at whatever length you want. What do you think your main contributions have been?

DJ: First of all, my career has been unusual in one way. It has been a little counter to the current. I’ve done a number of things at different times and I haven’t done any one in great depth. I’ve started things and dropped them, for better or worse. For example I was one of the very first people interested in the psychobiology of premenstrual tension. I think this was an important contribution; I wrote a paper, I think in 1971, called Monoamines, Ovarian Hormones and Premenstrual Tension, a Hypothesis. That was published in The Archives of Sexual Behavior. It predicted a lot of stuff that’s being expanded upon today. I postulated that the interaction of ovarian hormones and monoamines occurred and predicted that using serotonergic drugs would help premenstrual tension. Did anybody read it? I don’t know. I do know that in 1971 to 1973, in several journals, I discussed my work about what estrogens did to serotonin and to norepinephrine. Then I got out of that area and into the cholinergic direction with respect to mania and depression; that probably has been my best contribution. It stands on its own, but it also led to the use of cholinergic
drugs in Alzheimer’s disease. On the other side of the coin the serotonin “revolution” has swamped the whole cholinergic thing. However, if you look at the data, it goes along with the serotonergic findings. The cholinergic work is solid. When a cholinergic study has been done the findings are almost always supportive of the original hypothesis. I have a feeling someday there’ll be an integration between a cholinergic and a serotonin hypothesis. Also, there is my work on the idea that multiple neurotransmitters might interact to cause an outcome, rather than a single transmitter.

BA: An end point.

DJ: An end point caused by multiple neurotransmitters was something intuitively obvious, but most people were looking at only this or that one, such as norepinephrine in depression.

BA: It had not been expressed, probably, as clearly before.

DJ: Another important direction was the work with psychostimulants in schizophrenia. It was helpful in moving the field forward. To this day people are giving stimulants and looking at displacement of dopamine ligands in schizophrenia. Basically, that came from our earlier work. But, again, I’ve jumped into a field and out of it again. I feel that’s why, in a way, I went into research. So I could have a career where I wouldn’t have to charge patients and I liked the idea of being an innovator, getting in and getting out. Of course, that has a strong disadvantage, because the ethos in science is linear and in-depth. Still, I think I’ve been able to make a few contributions and that has been nice. Right now, I’m headed in a whole new direction, which goes beyond anything we have been talking about. I don’t know if it will be important or not. It has to do with underlying personality traits, like introversion or extraversion, openness, being judgmental, etc., and how these coalesce to cause a person to be a depressed, suicidal person or an alcoholic. Personality traits are heritable so there may be ways of profiling the genes in terms of personality rather than symptoms. I’m working on that and it’s a lonely direction. But, I like to innovate. I grew up in a left-wing family where my father was a violinist and my mother an artist; stagnation was anathema, and creativity and the arts were what they loved. Anyway, I think that my contributions have been several, and catalytic, as opposed to producing the final answer. Probably, if I didn’t get bored with a single topic, I’d be further along or better recognized in my career, but it’s been fun.

BA: How about the substance abuse work? We haven’t spoken about that and some of it has been important.

DJ: When I came to North Carolina as Chair of Psychiatry, one of the ways they recruited me was that I would be head of an alcohol research center.
I didn’t know much about that subject, but I had worked on methylphenidate and marijuana at San Diego and Vanderbilt. There was a lot of work going on at UNC; one area was to look at the physiology of calcium channel blockers in rats to see what alcohol did. My contribution was to look at this in terms of the behavior of rats that drank and didn’t drink and see what calcium channel blockers would do. A colleague, Amir Rezvani and I, used different behavioral models like the two-bottle alcohol preference test or place preference tests. This resulted in the development of a series of anti-drinking drugs that work in animals. Calcium channel blockers seem very effective in turning off drinking in rats and we established this over a period of years. One promising drug was kudzu, which in China is used as a hangover remedy; it did turn off drinking in rats, and we recently published that work with David Overstreet and Amir Rezvani. We looked at a thyroid releasing hormone (TRH) analog which turned off drinking and also published that. Many of these drug discoveries had theoretical reasons why they might work. We have a clinic in Chapel Hill where patients are detoxified and then go out in the world. They don’t get much treatment, so it’s a naturalistic setting and I was looking at what personality variables caused them to go to AA or start drinking again. I found that the TPQ persistence scale is important in helping to prevent relapse over the short haul. Shyness, introversion, as one might expect, is one variable that keeps them from going to AA meetings. Another thing we did was to look at the relationship of liking sugar to alcoholism. Drs. Overstreet, Kampov-Polevoi and I showed that “alcoholic” rats preferred ultra-sweet solutions and couldn’t stop drinking them, so I suggested we try this in humans. Kampov-Polevoi, J.C. Garbutt and I were the first to discover that indeed alcoholics select ultra-sweet sugar solutions, something we are now publishing. Most of our work has not been tried in people, but our calcium channel blocker work has been. Demet, at Long Beach VA Hospital, has done a preliminary study of giving isradapine, a calcium channel blocker, to alcoholics. It appears to work better than naltrexone.

BA: That’s very striking.

DJ: David Overstreet, who joined us in 1990, is a pre-clinical investigator, like Rezvani. David developed a genetically bred hypercholinergic rat. At my suggestion, we’ve done a lot of work looking at that as a model of depression. We have studied what happens to serotonin, to GABA, to dopamine and norepinephrine; all the neurotransmitters we consider relevant targets for depression in these rats, and most of them are perturbed, some quite profoundly. So, that’s what we’ve been doing in the alcohol center. I’ve ceased to be the head and don’t do as much with alcohol anymore.
especially since I’ve gone into the personality direction. Once again I’ve jumped ship!

BA: Like a gadfly! But one that leaves its mark!

DJ: We’ll find out.

BA: We’ve covered some of your changes in jobs. How about your philosophic ideas about research?

DJ: I have mixed feelings about that topic. We have become perverted as a system, at the national level, in our own minds, and in our universities where we do most of our research. The value system has become money and technique bound, as opposed to discovery bound. Although I’ve had grants over the years, I think that value system is sick. “Productivity”, as it’s now called, should not be based on whether you get a grant or not, but on whether you make a discovery. How many millions of dollars your department brings in should not be the issue. It should be to ask, “Did anything come of the work”? We tend to go down the same tracks in science because we review each other. If you’re doing what I like to do then, of course, I approve of it. It’s a shame that there isn’t stable funding for people to be creative, rather than project bound. If you’re creative you have to prove your idea before you can get funded, and that’s too bad. If I were able to redesign the world, it would be to take the same amount of money and divide it into modest little grants. This could help some to creatively do their work and see what happens; have more freedom. I’m not wide open to everything, but I feel that technique, prior proof, and rigor often trump creativity. For example, the grant committees often focus on using the perfect rating scale and getting high $\kappa$s instead of thinking about what is useful. We’ve thrown away a lot of things that are important in research by worshiping the God of obsessionality. On the positive side, if you throw a lot of money at something, usually you find something useful. Certainly, that’s happening in AIDS research and in Imaging. We have millions going into gene projects. I’m sure we’ll find some relevant genes one of these days and figure out what they do. But, I do think that the person who wants to look in a decidedly different direction is often considered “out to lunch”. I may be speaking for myself, though I haven’t recently competed in the grant area. If I did, it would be harder for me than if I followed a straight line, like taking the next step in exploring the cholinergic nervous system in depression, looking at genes and muscarinic receptors or imaging the limbic system after physostigmine infusion.

BA: And the more high tech methods are available, the more they’re expected to be incorporated in your projects and the more expensive they are. You
cannot do them by the “sweat of your brow” any more. You need a lot of funding for that kind of stuff.

DJ: I purposely decided to pick personality as a direction. I was fascinated with that ever since my NIMH days when I studied manic interpersonal interactions, but this area is something I can do at a very low tech level. Basically, I need a computer, a brief case and maybe half a lab tech.

BA: You don’t need a PET scan.

DJ: No but I may try to get one someday, or hope someone else scans the brains of introverts or clones their genes. We’ve made an industry out of this whole thing, and what’s come of it is often interesting and sometimes helpful. But some of the better discoveries lately, like the mood stabilizers for bipolar disorder, didn’t come out of some high tech device. They came out of somebody making clinical observations; those are very important and undervalued. We have gone overboard and embraced a value system that’s high tech and money oriented that has perverted the fun of it all. But in the meantime I’m not having a bad time myself!

BA: Is there anything you’d like to elaborate further on?

DJ: One of the questions on your list is how academia has treated you? I feel academia has treated me very well. The one down part of my career was when I was a Chairman of Psychiatry from 1986-1994. That was in part a pleasant experience. It was fun to be the center of attention, but it was very stressful, unpleasant and business like most of the time. Otherwise, from my point of view, my career has been a really good one. I’ve been very happy and it’s been great fun. I’m not sure where it’s going to go next. I find being a psychiatrist and a researcher enjoyable. I used to say that I’d never worked a day in my life. I do feel I worked when I was a Chairman, but since and before then, it never felt like work or that I was doing it for money. I didn’t feel that was my job. Somebody was paying me to do things I probably would have done as a hobby. I still think its fun but it’s a little rougher for younger people, as we become more economically driven in academia.

BA: We feel very similarly. Research still beats work!

DJ: That’s right. Thanks a lot for interviewing me.

BA: It’s been a pleasure.
SK: I am Stephen Koslow interviewing Doctor Marty Katz for the International Archives of the American College of Neuropsychopharmacology. I am going to ask Doctor Katz to address his life, career and the impact that he has had on the field and the ACNP. To start with can you give us an introduction to your life?

MK: I was born in Brooklyn, New York and grew up there. I received my degree at Brooklyn College, majoring in chemistry and engineering, but switched over to psychology after coming back from the Army. The shift was partly because it was determined I was color blind and had difficulty with titration and other lab operations in chemistry. My first interest then was in combining these two fields. Psychology was very exciting at that time and was just beginning to develop as a science. After I completed my undergraduate experience I went on to the University of Texas where I took my degree in psychology, with physiology as a minor. With that kind of background, I received my PhD in psychology.

SK: What made you interested in adding drugs to the formula?

MK: My first job right out of graduate school, where I had been studying the interaction of self esteem and memory, was at the Texas Women’s University. It was for a post doctorate year as an assistant professor. The school was run by a Dean who was an expert in physiology and nutrition science with grants from many sources which provided support for my position. In a very nice way she said we had a wonderful grant from the Florida State Citrus Group Commission; they were interested in the effects of vitamin C on intellectual functioning. I felt that was very intriguing but would not qualify as a serious experiment. But, she convinced me I could be a great help to the chemist and nutritionist if I would design a study on the effects of Vitamin C on intellectual functioning in children. She had a couple of grade schools where kids who were nutritionally underfed could have their ascorbic acid levels raised by orange juice every morning. In the kids who were nutritionally well fed it was believed that increasing ascorbic acid would not have an effect on their nutrition or performance so they could have the same orange juice which would act like a “placebo”. Since the kids didn’t know who was nutritionally deficient and who was not, and everyone had the same treatment, it was like a “double blind” study. The expectation was that kids at an adequate level of Vitamin C would not be improved by the orange juice, but the ones that were deficient, would. I thought this was an interesting idea, but
too far out to be taken seriously. Strangely enough, the results showed the kids who had the lowest ascorbic acid level that was increased by the orange juice supplement, had a significant improvement in their performance IQ tests six months later. It shook me up a bit and I developed more respect for the effects of nutrients and chemistry on behavior in children. Later, at a regional research conference, I related this story to Jonathan Cole.

SK: Who was Jonathan Cole at that time?

MK: Jonathan Cole was just about to become the head of the new psychopharmacology group at NIH. The Congress had agreed to give the NIH two million dollars because of the introduction of chlorpromazine for the treatment of schizophrenia and the excitement around that. It was the beginning of the psychotropic drug era and they were hoping to stimulate that whole field into more research in psychopharmacology. Jonathan, in his creative way, saw the Vitamin C experiment as a kind of double blind drug study and carried that thought back with him to Washington. A year later, I took a job in the Neuropsychiatric Research Lab at the VA in Washington, to study the efficacy of psychotherapy which was my main interest at the time. It turned out to not be very satisfying but I learned a lot about the technology of evaluating change in mental patients. Strangely, in the nineteen fifties, psychiatry and psychology didn’t know how to evaluate treatments. They had been experimenting for thirty years with open studies that did not have proper controls or adequate methods for measuring change so there was no definitive test for a treatment. But now a model had to be developed to deal with the introduction of this new drug to the field. When Jonathan offered me a position at NIH, I was very reluctant to take it because I didn’t want to continue in government. But, I did look at the Institute and was overwhelmed by the nature of the NIH operation. It was, for scientists, a thing of beauty. It had wonderful laboratories in which scientists were able to work on the problems they considered important, and in this new program, were the new drugs that would change psychiatry and the treatment of mental disorder forever. I immediately perked up and realized I was being offered something very, very good.

SK: So, you were being recruited to do research on psychopharmacology?

MK: I was being recruited to help the NIH develop collaborative clinical trials of the new drugs. So far they had only very small studies demonstrating effectiveness, so what was needed was a large scale study across the country of chlorpromazine and variations of it in schizophrenia. Jonathan Cole was in charge of developing this major study and he needed help with the development of methodology and research design. My association
with the collaborative study was only part time. My real job was working with a Psychopharmacology Advisory Committee initiated by the NIH that was made up of leading scientists in the country from many disciplines. They were to establish this new science, and to guide the development of the field.

SK: Do you remember who some of those people were?

MK: The chairman was Ralph Gerard who was a world famous neurophysiologist. He had started an Institute of Mental Health at the University of Michigan, and was a very interesting figure. The people on the committee included Seymour Kety, who was the head of intramural research at the Institute of Mental Health when I was there. Sam Greenhouse, a statistician and expert on the design of clinical studies, Nathan Kline, probably the leading proponent of the new drugs in the treatment of schizophrenia and mainly responsible for generating that two million dollars for research, Lou Goodman, a famous figure in pharmacology and author of one of the outstanding texts in that field, and Lou Lasagna, a great pharmacologist then at the University of Rochester. They were some of the most impressive people I have ever come across and I was in my late twenties at the time. I was to be the executive secretary working with Ralph Gerard, the Chairman; essentially I was the administrator of the operation and still very wet behind the ears. I was also overwhelmed in the presence of such great scientific figures. They must have thought I was pulled from the ranks of some prestigious scientific society because they treated me with all of the respect I didn’t deserve. I had that job for two years and Jonathan Cole and the staff managed to get those collaborative programs started and obtain the funding for a wide range of basic and clinical research in the field.

SK: Were the collaborative programs all on schizophrenia or also in other research?

MK: They went beyond schizophrenia, for mental disorders generally. But, the first successful drugs in treating mental disorder were the ones in schizophrenia. By nineteen-sixty the antidepressant drugs made their entrance as did lithium. These drugs came in a wave and we witnessed a small revolution in the whole field of psychiatry and the treatment of mental disorders.

SK: So, this was your first foray into psychopharmacology and initiating major research programs at the Federal level. Was this about the same time the ACNP started and did you get involved with the ACNP?

MK: The year it started was 1961 and I became a member shortly after that, in ’62, or ’63. I wasn’t a founding member but I was one of the first. The society was quite small at the time and had relatively high standards for
membership based mainly around the great clinical drug developments and basic work underpinning it. It was very well balanced in terms of basic and clinical work and seems very different from today where the balance has shifted well over into the basic area. The clinical side seems to be much more reduced, but at that time it was central to the society’s action and mission. One of the people on the Advisory Committee I didn’t mention on the clinical side was Heinz Lehmann, who introduced chlorpromazine to North America. There were all these famous people around and it was an inspiring time.

SK: What other significant things did you do that were important for developing the field of psychopharmacology?

MK: I worked in the field of psychopharmacology directly for a ten year period with Jonathan. I went from assisting and doing research on the collaborative study to development of clinical methodology for drug evaluation, a particular skill that I had. I was assigned to develop methods of measurement of long term, rather than short term effects, of the drugs. Out of that came a set of adjustment scales that have been widely used since and were used to study the effects of drugs on schizophrenia a year later. I put extensive time into that involvement. My other assignment was in research on diagnosis and I was asked to develop a national conference aimed at shoring up the standard diagnostic system in psychiatry, which was very wobbly. There were many systems at that time, and much controversy about which one was better. There was no such thing as an operationally based system, there were several clinically based systems related to different theories and clinicians would just be comfortable with one or other system. So we tried to develop a scientific approach, one that would be acceptable to clinical investigators, and would meet research standards. We couldn’t worry about the whole field of administrative, practical and clinical demands, but we had to worry about diagnosis for research, because, as scientists know, the results of any one study are only relevant to the kinds of patients in the study. If they can’t be defined in a systematic and precise way, nobody knows who the treatment is effective for and the results cannot be generalized. We were aiming toward a system for diagnosis based on operational definitions. I was given the job of creating a conference on the state of the field and the problems preventing the development of this new system. The conference was called the Role of Methodology and Classification in Psychiatry and was international in its scope. In the course of it I developed experience in putting together large conferences. We had some formidable people at those meetings. I remember Max Hamilton, famous now for the Hamilton Depression Scale, being at that first meeting and other important figures from Great Britain,
other countries and the United States. It resulted in a volume that had some impact at the time, published by the government. The volume was called *The Role of Methodology and Classification in Psychopathology and Psychiatry*, co-authored by myself, Jonathan Cole and Walter Barton, executive director of the American Psychiatric Association. That conference was a success and we like to think it played a role in research over the coming years which eventually led in the mid-1970’s to the development of the current DSM classification scheme. On another track, during the late 1960s, we initiated a special studies program at a nearby prison and conducted experiments designed to test new methods in “normal subjects” for the evaluation of the effects of LSD and other drugs. That program lasted several years. People like Irene Waskow and Carl Salzman, who was just out of residency, participated. I had started out, when I first moved into psychopharmacology, studying these kinds of drugs and my first paper on the psychological effects of LSD type drugs was at a symposium at the Army Chemical Center in Maryland, way back.

SK: Was that one of your most significant papers?

MK: I don’t think it created great waves. LSD is, even today, somewhat of a mystery. What it does to the mind is very difficult to describe in any sensible way although lots of people have tried. LSD has a great impact on various psychological functions, as remarkable in the chemistry of brain function as chlorpromazine, but from an entirely different direction. But we have never been able to study it in the way we would like because of all the problems it brought with it, the untoward effects and the possibility of permanent harm. These things scared people off research and the government stepped in to shut down most of what was being done. So, a great mystery remains; decades later we still do not have any answers. We did turn out a couple of important papers, one published in the *Journal of Abnormal Psychology*, back in the 1960s. We also did work on tetrahydracannabinol and set up new methodology for the psychological study of these drugs. We added to the little objective knowledge on their psychological effects. We developed perceptual methods and questionnaires that were designed to test these exotic drugs and one of them is still used today. So the laboratory did make some valuable contributions to our current knowledge base.

SK: You were there at the introduction of all the significant psychotropic medications and treatment regimes for mental disorders. What else did you do while you were at the federal government to move these areas forward?

MK: The work I did intensively was, for example, the application of behavioral methods to articulating the clinical and psychological components of schizophrenia so that we would learn which aspects the drugs affected.
We were able, in the collaborative studies, to describe the classification of schizophrenia in a different way, in accord with a behavioral typology. This was intended to make the diagnostic system amenable to determining which types were helped by which drugs. I didn’t get into depression research during that period, because I focused my research on schizophrenia and the psychedelic drugs. These directions were interrupted in 1968 when I went on a sabbatical year from the National Institutes of Health to the East-West Center in Hawaii to pursue another interest. That had to do with a very different kind of problem; the impact of culture in shaping the pathology of schizophrenia. Jonathan Cole was moving on and things were changing about what course psychopharmacology would take at the National Institute of Mental Health. I wasn’t sure I wanted to remain at the Institute; I was ready to move on. What occurred, however, was that the Institute was reorganized and a new branch was established that several of us had promoted. It was a more broadly based group designated as the Clinical Research Branch. Many of the staff thought that the psychopharmacology program had been instrumental in creating methodology that was needed for study all treatments of mental disorders. The program had moved the whole field forward, not only the drug field, but every aspect. We were now ready to attack all the problems in clinical research, not only the behavioral aspects, but the role of neurochemistry in the nature and etiology of the disorders. The study of the neurochemistry of depression and schizophrenia could proceed on its own, not necessarily associated with drugs. The Clinical Research Branch was to be dedicated to studies of the basic psychopathology and treatment of all mental disorders, apart from those which continued to evolve in the drug world. The new branch had a chief who stayed for the first year, then because of some conflict with administration, had left. Louis Wienckowski, a formidable leader at the NIH took over the division of extramural research under Stanley Yolles, the director of NIMH, and offered me the position. It was a wonderful opportunity to get involved in a whole array of new research problems and I was only too eager to move up and take it on. So when I returned to the Institute in late 1968, I took on that new responsibility and position.

SK: How long did you stay in that position and what were your most significant accomplishments during that period?

MK: From 1968 to 1978 and we did some remarkable things. We took the collaborative strategy designed to evaluate new drugs over to basic research and applied it to study the psychobiology of depression. The big problem in clinical research is that the subjects of study are human beings. The kind of research we did required large samples, not like in the laboratory,
and you can’t get those unless you dedicate yourself to five or ten years of accumulating data and overcoming, at the same time, many practical obstacles. We learned from the early drug studies that the collaborative mechanism could help get beyond these obstacles. Soon after I got there we convened a national conference on the biology of the depressive disorders. New theory had postulated a neurochemical basis to depression; it was viewed by many at that time as highly speculative. Depression was a disorder recognized for centuries and all of us who studied it in the pre-drug era accepted it as a terrible illness, but were convinced that its roots were 90% psychological, brought about by developmental dysfunction, specific environmental stresses, or variations on these themes. The idea that chemistry could create depression and changes in chemistry could resolve it, was viewed as a pipe dream, a notion that lacked any substantive base. The drug revolution changed that whole idea, and out of that came some very fruitful hypotheses about chemistry and depression. The Williamsburg conference, held in 1969, took on all these issues and came up with recommendations for the kind of research that needed to be done in the future. So in a way, the conferees, the experts from various disciplines were providing my new Clinical Research Branch, comprised of psychiatrists, psychologists and pharmacologists with a guide to what could be done in the future if we had the resources, the backing of the Institute and the energy to pull it off. Fortunately we had the right people at the right time to create these collaborative studies. One area, biological studies, was chaired by Jim Maas, one of the classic scientist psychiatrists of his day, a formidable man. He would take on the testing of biochemical theories, and as part of that program put together the first experiment to include the proper controls, a wide range of methodology, and the large patient sample required to test hypotheses about chemistry and depression, utilizing the collaborative mechanism. I don’t think there are many examples like that in the literature because it required a range of investigators, the very large patient sample, several hospitals and great expense. It seemed too unwieldy to pull off but a lot of innovative people made sure the thing worked. It took people like you Steve Koslow and Steve Secunda, a psychiatrist in private practice today, as well as Tom Williams who coordinated the Williamsburg conference and enlisted a number of very unusual people to participate. The Biological Studies program represented one side of our overall effort, the Clinical Studies Collaborative program, represented the other. The clinical study was chaired by Gerry Klerman. That study saw as its first task the development of an objective, reliable diagnostic system in which categories would be operationally defined, in accord with the Research Diagnostic
Criteria of the St. Louis school. That had to be our first step in testing new biological theories or in researching the nature of depression; to generate a system for diagnosing and classifying disorders that was generalizable, one that when used in research would guide the selection of patients, and make the results applicable to patients at large. So that had to be done immediately. We then contracted with Jean Endicott, Bob Spitzer and Eli Robins to refine the Research Diagnostic Criteria, the operational criteria they created that formed the basis for the DSM system. Bob Spitzer became the chairman of the DSM Committee for Psychiatry the following year and created the first operationally defined research diagnostic criteria system applicable to the whole field of psychiatry. You see, we are very modest; we take credit for all of these things!

SK: During your career you have done a lot of things; your publications include classification, diagnosis, psychopharmacology, methodology of assessing behavior and the cross-culture area. Do you want to comment about those areas as they relate to your general interest in mental disorders and quantification of psychopathology?

MK: I do want to say something about the cross-cultural study because it does link to these other fields; although it may not seem on the surface to do that. It is an old interest of how cultures impact the development of mental disorders; for example how Japanese schizophrenia is different from American schizophrenia. It’s hard to show this and to see what the real factors are without doing the research and one of the contributions of the adjustment scales for evaluating the long-term effects of drugs was part of this. I had been asked to create that method to study the social adjustment of patients with schizophrenia a year after they had a drug or some other treatment so we would know how well they were functioning in the community. In so doing I developed a way of describing abnormal behavior in people, in language amenable to a lay person, so you could describe the pathology of a patient just as it appears in the community. It would not be through the eyes of the expert but through those of a lay person. Based on my earlier interest I developed that so it could be applied in different cultures to get an idea of what the everyday behavior of a certain kind of abnormal person was in that culture. Then we could use it to compare the everyday behavior of different ethnic or cultural groups. The laboratory for doing that research was in Hawaii where they have many different ethnic groups well represented. They are all very different, Japanese, Filipino, Native Hawaiians, and Caucasians. We set up a research program for studying these groups to show the differences and similarities in social behavior across “normal” and mentally disturbed subgroups. The method provides a view of how people related in the
community, going beyond what a doctor sees in 15 minutes or half hour interview, and how the drug treated patient appears a year later. The method worked very well with regard to these issues and was eventually carried over to the World Health Organization epidemiological studies. I also worked with the World Health Organization in a study that compared schizophrenia in Japan to Nigerian, Indian, and Hawaiian communities. We published an extensive report in the *Journal, Culture, Medicine and Psychiatry* in 1987. At that point I had to leave the field because of other pressing involvements. But it was all part of the same fabric; one gets interested in the interaction between culture and behavior and then the interaction of chemistry and behavior. When we talk about mechanisms of action of drugs it leads me to this other area; the continuing problems which surround the clinical trials of new drugs. What is meant by behavior in these clinical trials is the range and number of symptoms that are measured on a Hamilton Depression rating scale. That type of study tells us nothing about the profile of drug-induced behavioral effects. In the collaborative studies we were able to make links between neurochemical drug actions and behavior more directly. There was a study by Redmond and others in which cerebrospinal fluid changes in the concentrations of neurotransmitter metabolites could be examined in relation to the way certain behaviors change. To do that you have to have specific measures of affect and behavior for example, anxiety, anger, hostility and measures of motor behavior; you couldn’t just measure the severity of symptoms of depression. You have to develop measures of these behavioral factors. Then we demonstrated, something few investigators have been able to show, a direct interaction between a change in the chemistry of the neurotransmitter metabolites and specific behaviors in the mental disorder. These results have been published in the *Archives of General Psychiatry* and in *Neuropsychopharmacology*. That is work I am very proud of. It is something that was always in the back of my mind when we were working on the collaborative studies. As far as carrying it over, we’ve written a few articles on important aspects of the process of behavior change affected by drugs. That was only possible because of our capacity to measure specific behavioral facets of the disorder. As a strong example of how these measures assist understanding of how the antidepressants work, we asked what the first actions of these drugs are on the depressed patient. Is it, as most believe, to reduce depression as a whole or is it to reduce two major aspects of the disorder, anger and anxiety. Those who are deep into this field know that the serotonin system is associated mainly with impulsive aggression and anxiety. It makes sense that these drugs, if they are affecting serotonin level, should be impacting anxiety
and anger and you would not be surprised that is what they do first, before they affect other behaviors and moods. A selective noradrenergic agent, like desipramine, also impacts anxiety, but it first activates “arousal”, a motor function, so retardation is reduced. Should we not expect that a selective norepinephrine agent would relate to motor activity, arousal, when we examine studies of its association to these behaviors in the basic literature? So why have we not completed the story about how these drugs operate therapeutically in patients? We have tried in certain ways but for some extraneous reasons, it doesn’t seem to take. There has been little examination for years, of the series of behavioral events that happen in the first week when you give these drugs. Clinical trials appear to dictate that the investigators only want to know what happened in four weeks or six weeks since that tells you whether the drug is effective as a treatment. If you ask where the intensity of my effort has been over the last few years, it’s been on studying the interaction of chemistry and behavior that underlies how drugs work. Until we lay out that fabric and understand it we are not going to develop any better drugs. As long as we adhere to the mechanical clinical trial method for information on how drugs achieve their therapeutic effects, we are not going to learn anything new. Sorry to say that, but I think it’s basically accurate.

SK: You came in at the beginning and created the basis for the field of psychopharmacology from the federal perspective of funding and stimulating people to ask the right questions.

MK: I helped.

SK: You have to pat yourself on the back for creating a tremendous field of study to understand and treat mental disorder.

MK: It has to do with hanging around long enough. You can actually get something done!

SK: Now you have to hang around a little further to finish it off.

MK: That’s a good idea.

SK: If you had the strings to pull to open up additional areas, what do you think the most important thing to do is? Can you speculate?

MK: I have written an editorial recently in the *Journal of Clinical Psychopharmacology* on the need to dispel some of the assumptions that underlie current clinical trials. I think it was Jules Angst, the great European psychiatrist, who called them “myths” in the field that continuously form or control the basis of what we do. For example this notion that an antidepressant takes several weeks or months to act is one of the myths. It is an assumption that has been invalidated by many studies, by three recent meta-analyses, by independent studies and by editorials from investigators in other countries. It’s time to let this delayed onset
notion go, and to accept the evidence that antidepressant effects start to happen in a week, and that the main reason there is controversy and confusion is that investigators confuse recovery, with improvement in certain aspects of the disorder which represent specific early actions of the drug. If we were studying actions on behavior we wouldn’t be talking about full clinical response. You would want to know exactly what happens to behavior immediately, because effects on the neurotransmitter systems have been shown to be immediate. Where did the idea that nothing happens for several weeks come from? It is based on studies which were very influential in the early 1980’s and despite those studies having significant shortcomings the results are in every textbook. Since few have examined drug effects on behavioral facets of the disorder during the first two weeks, the field has been late to uncover that actions on behavior and improvement, begin in the first week.

SK: So you think this is more of a definitional issue about what recovery or improvement mean?

MK: If you want to know how the drug actually works, something that even at this point in the development of the field is not clear, you have to examine the entire therapeutic process; that means you have got to look at the actions in detail, particularly during that first period. It is understood in neurochemistry that all elements of neurotransmitter action must be examined. They are examined at every step of the way. Why have clinical trials not examined drug actions in terms of elements of behavior? Why not compare patterns of change with other drugs? Another problem is assuming that all classes of antidepressants we have now are initially affecting the same symptoms. That’s another of the myths in the field. No matter that the different drug classes have different neurochemical effects, they are assumed not to have differential effects on behavior. But the evidence shows that they do have different effects on behavior. We published results on this as other people have. There is an article we wrote about ten years ago based on our experience with the collaborative study that I believe should have more of an impact on current thinking in this area. One conclusion that Jim Maas, the chairman, and I came up with was that the DSM system has become an impediment and could be a misleading influence on the design of future research. If we don’t transfer reliance on that diagnostic system to changes in behavior, mood and cognitive functioning we will never learn the nature of the elemental interactions between chemistry and behavior that determine what is going on in the therapeutic process. So it is necessary to place less reliance on the diagnostic system in the design of clinical and drug studies and turn to the components of the disorder.
SK: Thank you for all this valuable information. Do you have any concluding comments?

MK: I am troubled by the faddish qualities that enter this field from time to time, that take us away from attaining closure on issues I have talked about. The current interest in genetics, for example, is well founded and it is surely going to be an important area in the future for all of our research. However, we have not yet resolved critical issues in the underlying chemistry and behavior and should continue that pursuit to achieve closure on understanding the basic mechanisms of action of these drugs.

On another subject I would like to see us getting back to examining the effects of psychedelic agents; they offered so much promise not only in terms of generating new classes of drugs, but in opening up the still mysterious processes of the mind to scientific study. They had such unusual effects on memory, perception and learning, but we have no way of knowing what they might tell us about the mind, its potential and its limits, if we don’t pursue further work in that area.

SK: Terrific! Thank you, Marty. It has been a lot of fun listening to your life experiences.

MK: Well, I appreciate your interest Steve. You gave me the opportunity to say everything I wanted to.

SK: Good, great, thank you.
JD: This is an interview with Donald Klein for the ACNP history project. I’m John Davis and I’d like to start out asking when you were born, a word or two about basic demographics and then get on to medical training.

DK: I was born on September 4, 1928 in New York City where I lived most of my life. The big turning point was going to the Bronx High School of Science, a city run specialty school, where you had very intensive training and a remarkably smart staff. My father, whose education only went to the high school level, was a very intelligent man; we used to go to museums forever.

I wanted to be a scientist all my life. I wasn’t sure what kind of scientist, probably chemistry initially. I went to college at fifteen and stumbled on Freud who was talking about things I was interested in at the time, sex and aggression, which made me want to be a psychoanalyst. I found that to be a psychoanalyst you had to go to medical school so as to become, what turned out to be non-existent, a research psychoanalyst. I graduated Colby College in 1947, magna cum laude but. I couldn’t get into medical school, although I had been number one in my class. It was a combination of things. It was the end of World War II and veterans were flooding back and they got priority, which was understandable. There was also a fair amount of anti-Semitism at the time. I tell everyone at Columbia that they turned me down twice. I spent a year in graduate school at NYU, in biochemistry and endocrinology, which turned out to be extremely useful. It gave me a running start on what was necessary to be a systematic scientist. After that I was accepted to medical school, worked as a research laboratory technician for my friend Norman Kretchmer who went on to be Director of NICHD, and did a rotating internship in the US Public Health Serice. I intended to stay in public health during the Korean War, but they terminated me after my internship. In July 1953 I ended up as a first year psychiatry resident in Creedmoor State Hospital, which was a six thousand bed jail, with non-existent psychotropic medications. I had no experience with psychiatric patients but they put me in effective charge of the admitting unit and the male acute ward. I stayed there for a year and saw a lot of amazing psychopathology, things that people just don’t see anymore. Then I went back into the Public Health Service and, by good fortune, landed at the 1000 bed USPHS Hospital for Opiate Addiction in Lexington, Kentucky. The inmates were 70% black, 80% federal prisoners and 20% volunteers for treatment. I ran the 70-bed
admission/methadone withdrawal unit. I had no experience in addiction but was put in charge of the Admission and Withdrawal Unit,

My training was going on rounds once with the departing director. This jail was run by three supervising psychoanalysts who tried to turn it into a model, based on Chestnut Lodge. The 50 white female patients who were in psychotherapy had both a psychotherapist and an administrative psychiatrist, who dealt with realistic issues, things like parole. I had the good fortune to meet Abe Wikler and Harris Isbell, who were running the most advanced human experimentation program in the world, funded by the Public Health Service.

The FDA had approved meperidine (Demerol) as a non-addicting narcotic because the strain of dogs they tried it on didn’t get addicted. But, humans did and that caused a tremendous scandal, a prefiguring of our current post-marketing problems. They realized the only way to test possibly narcotic drugs was on human beings and species wise that’s probably correct. They figured that prisoner addicts, who had served ten years in prison and who volunteered, would be suitable subjects. It was a remarkable experience. I had no formal research role but was able to participate in the early studies of LSD, reserpine and chlorpromazine.

I was put in charge of the psychotic unit which was for WWI veterans, who had become psychotic before there was a VA. They were on something called the Executive Order. They had been hospitalized forever. Although they had received excellent rehabilitation care with excellent nurses most were mute, incomprehensible or grossly paranoid. I decided to give them all chlorpromazine, 200 mg a day, which was a big dose then. One of them, after about six weeks, came to me and said, “Hey Doc, when am I getting out of here”? It was the first time he had said anything in thirty years; it was very convincing that chlorpromazine was not just a chemical straight jacket.

I went back to Creedmoor, where I finished my residency and became a member of the Creedmoor Institute for Psychobiological Studies which was initially run by Arthur Sackler, but had been thrown out by the Creedmoor Director on entirely political grounds.

I got involved in a variety of things. For a year I was the Clinical Director of a psychoanalytically oriented clinic for six families with autistic kids. I was in charge of play therapy for a pair of identical autistic twins as well as the father’s group therapy; I asked my supervising analyst how the mother got the twins to walk on their toes, and he told me that was resistance. Later, the remarkable Loretta Bender came to Creedmoor to run child studies. Eventually, the State closed our clinic down; our patients all got hospitalized despite their intensive care, and we went
into geriatrics and early studies on anti-psychotics. We picked, as our first antipsychotic, mepazine (Pacatal), because it had anecdotal reviews of being a terrific agent. We did a double blind randomized “add on” study. Patients who were already on anti-psychotic medication were randomized to either placebo or mepazine supplements. We found nothing. The drug, as far as we could see, just did not work. We published the results and a couple of months later there was a large VA study published that had used phenobarbital as the placebo, mepazine and a couple of the other anti-psychotics. They found the other anti-psychotics were far better than phenobarbital, but mepazine was only marginally different from phenobarbital and much worse than other antipsychotics. The drug was withdrawn from the market; I think it’s the only phenothiazine ever withdrawn. This was way before the Kefauver-Harris amendments and the efficacy requirement for marketed drugs. We also did a large study on dicumarol vs. placebo vs. no treatment in hospitalized, demented patients aged over sixty that was published in the *Journal of Chronic Diseases*; it was one of our first papers. We found they lived longer on dicumarol, but their mental status didn’t get better. We did a number of other studies of modest interest.

The big shift in my life came in 1959. There was an opening at Hillside Hospital, a two hundred bed psychoanalytic hospital of the Federation of Jewish Philanthropies with a Research Department of Experimental Psychiatry. The hospital director was Lew Robbins, a training analyst from Topeka, an extremely nice man with an open mind, who said very early on that we didn’t understand these drugs but should try to figure them out. I went to work for Max Fink, who ran the quite unique Department of Experimental Psychiatry. Hillside was a non-academic hospital, affiliated with no medical school. But it was an unusual place because it had a research tradition. Max had done excellent work on ECT and was a terrific mentor, guide and relentless critic. He sent back my first attempt at a paper about seventeen times, telling me to fix this, fix that and he was right. We got involved with extensive pilot studies of chlorpromazine and imipramine for two years doing what would now be called early phase two studies, We were able to study patients for optimum dosage, running the dose up and down over time, finding out how long the drugs took to work, how to deal with side effects, who the drugs worked or didn’t to work on. That was a Utopian opportunity; one of the biggest missing pieces in current psychopharmacology is adequate phase two studies. One of the reasons that we don’t have any longer these type of studies is that industry can’t use them as definitive for the FDA; they don’t count. Another reason is that drugs are rushed through so as to have maximum
patent protected marketing monopoly. Eventually we wrote two papers, one on about a 100 patients treated with chlorpromazine and another 100 treated with imipramine. We described the various patterns of response to the medications. I developed the notion of pharmacological dissection since we had no clear idea about how people were grouped diagnostically. When a group of patients had a similar positive or negative response to medication they could be categorized as pathophysiologically similar.

JD: How did you get that unusual idea?

DK: It was based on my experience with imipramine when it was not yet marketed. The relationship between drug houses and investigators was entirely different than it is now. As I recall, Max Fink was able to deal with Geigy so they gave us a lot of imipramine and said do something useful with it and let us know what you find out. We had arranged with Lew Robbins that for this two hundred-bed hospital, with an average length of stay of ten months, that I or Max were the only people who could write orders for medication. The residents had to call us first, and say Mrs. Jones is schizophrenic and we want to put her on chlorpromazine, 200 milligrams a day. That gave me the invaluable opportunity to ask the resident, why are you doing it now? After all, the patient has been here nine months and has been schizophrenic all along. The resident would say it was to lower anxiety which was interfering with psychotherapy. Then I would talk with the supervising analyst who told me the resident was doing a bad job in psychotherapy so had to fall back on medication. Questioning the ward staff revealed a rising level of discontent; anything would be better than aggressive outbursts. The patients would say they had given up on going home and were willing to try anything. I would prescribe the chlorpromazine and follow the patient up weekly, doing whatever the treating staff wanted me to. It was the world’s best learning experience. Patients getting the same drug were having very different reactions. Finally, at one point, we knew that imipramine was a good antidepressant but it also had some funny antianxiety effects. We had a patient who was diagnosed schizophrenic and had responded badly to chlorpromazine so we put him on imipramine. The patient said that meant the hospital had lost all hope or they wouldn’t put him on an experimental drug. I slowly raised the dose and after two or three weeks the patient was complaining incessantly that the drug was doing nothing for him. The therapist didn’t think much was happening; the supervisor was certain that nothing was happening but then the ward staff tipped me off. This patient had been there for ten months and kept running to the nurses’ station saying he was dying. The nurses would hold his hand and reassure him he was not, that it was just terrible anxiety and there was
nothing wrong with his heart. After ten minutes or so, the patient would wander away but would be back a few hours later again complaining he was dying. Now the nurses said he hadn’t done this for the past week. So, I went to the patient and said, “I understand you are feeling better”. He asked, “Who told you that”? Well, I said, “the nurses did”, and he replied, “What do they know”? So, I said, “Isn’t it true that you have been running to the nurses’ station for months but you haven’t done that this week”? It really stunned the man, because he hadn’t thought about that at all. When I asked why he had stopped he said he finally learned they couldn’t help him. I asked him how he had managed to learn that this week, He swiftly replied, “Well, you have to learn some time”. We were able to figure out later he was suffering from what I called a “three layer cake”. He got spontaneous panics, ran for help; developed tremendous chronic, anticipatory anxiety, and “phobic” avoidance, where he wouldn’t go anywhere unless help was easily available or without somebody with him, even in hospital. Now, this is recognized as agoraphobia. He was tying his family into knots. On imipramine the panics stopped, so running to the nursing station also stopped. However, the tremendous anticipatory anxiety had not stopped so the phobic avoidance continued. That took time and exposure before it stopped. At that point, I realized that anxiety wasn’t a single thing, that here we had three different kinds of anxiety dissected out by the medication. That’s where I got the idea of pharmacological dissection; where patients’ symptoms and behaviors, lumped under the same label, became distinguishable and patients who looked similar but had different drug responses must have different pathophysiologies.

We later did a double blind placebo controlled study, randomized regardless of diagnosis - diagnosis was terrible at the time - to placebo, imipramine, or chlorpromazine mixed with procyclidine, an anti-Parkinson drug. The drugs were given in liquid form to prevent cheeking and patient knowledge of dose changes. We used a fixed-flexible dose aiming at 300 mg per day of imipramine or 1200 mg per day of chlorpromazine. These doses came from several years of pilot observations. We studied 150 patients and, then, did another 150 patients. It’s one of the largest single site studies. We were able to systematically validate that these drugs work in patient dependent ways. We found, by the way, that chlorpromazine was an excellent antidepressant. A handful of other studies by Leo Hollister and people in Europe also showed that antipsychotics for severe depressives really worked. However, that fit none of the current theories at the time, so it fell off the therapeutic and cognitive table and was killed by the recognition of tardive dyskinesia. The new brand
of antipsychotics, that don’t have much EPS, came along and some have found them useful in affective disorder. Somewhere along the line you, John Davis, came into my life. In the 1960s we became friendly, talking with each other at meetings and you told me it would be a good idea if we wrote a textbook.

JD: I figured nobody would read a textbook written by a resident, so I needed a good thinker and an experienced clinician and it went back to the papers you were just talking about.

DK: That textbook John and I wrote was the first systematic textbook on Diagnosis and Drug Treatment of Psychiatric Disorders. We had a discussion, about diagnosis broken up into psychoses, affective disorders and neuroses. For each category we had a complete systematic review of the literature which John did. It’s still one of the best reviews in the literature. That sort of extremely detailed literature review has been replaced by meta-analysis which is much worse in every way.

JD: The value of meta-analysis is that clinicians realize when there isn’t an answer. That encourages the clinician to use his intuition and may empower the patient to state their preferences, because it identifies where there’s literature and where there isn’t. Instead of the expert making it up, in our book, I put in the controlled studies and you put in the clinical wisdom, so we had both.

DK: It was a good book and I’m very pleased and proud we did that together. It came out about 1969.

JD: Yes.

DK: One of the funny stories I remember about the book was that after we worked four years on it I got a call from Williams and Wilkins who told me the book was bound and ready to go. The title of book was Diagnosis and Drug Treatment of Psychiatric Disorders but they had left the word “drug” out from the cover completely. When they called from the publishing house and asked, whether leaving out the word would matter, I blew up, of course, and they had to rebind the books and put a strip on the back, which regularly peeled off. The book had a heavy emphasis on descriptive diagnosis and was a forerunner of the reawakening of interest in descriptive diagnosis.

JD: Let me ask you about discovering panic attack by using pharmacological dissection. You identified a new disease and also its treatment.

DK: The point of pharmacological dissection is that when you note an unusually effective treatment in some sub-group of people you ought to identify and describe that sub-group. We also did that, later on, with atypical depression, which was an even a better story in some ways. I also worked closely with my wife, Rachel Gittelman Klein, and did early
studies on ADHD children. She’s still doing controlled follow ups on that same group that we studied in the late 1960s. Those children are in their forties now; she’s going through her third wave of follow up and now is getting brain scans on them with Xavier Castellanos. We have been able to follow-up particular interests for long periods of time; panic attack we have followed in terms of treatment, and lactate and carbon dioxide challenges. More recently we have considered a possible endogenous opioid deficiency. I just finished a study with Maurice Preter, trying to produce something like a panic attack in normal people. Lactate really doesn’t affect normals much but causes panic in panic disorder. Based on our theory, we hypothesized that interfering with the opioidergic system before lactate infusion in normal subjects would produce panic like symptoms. So we did a controlled study, randomizing subjects to naloxone prior to lactate, naloxone prior to saline and saline prior to lactate. We have a paper in Biometrics, of all places, showing that it’s only when lactate was preceded by naloxone that we got very marked tidal volume increments like those in spontaneous panic. So it’s suggestive but not definitive evidence. The next step would be showing whether this reaction is specifically blocked by antipanic drugs.

The other thing we have done that is interesting is in the atypical depression area, in studies largely carried out by the late Fred Quitkin. The prototype atypically depressed patient has a temporarily responsive mood, tends to overeat and oversleep, is very rejection sensitive, and has enormous fatigue or may have just one of these features. Comparing an MAO inhibitor, phenelzine, versus a tricyclic antidepressant, imipramine, versus placebo, we found in about six different studies that MAO inhibitors really work. The tricyclics are barely better than placebo and the MAO inhibitors are much better than the tricyclics. Jon Stewart went back over all the histories, just like we’ve gone back over the panic disorder histories, and found that in patients who had early onset, or chronic depression, tricyclics didn’t work at all; only the MAO inhibitors did. In people who had later onset or more intermittent depressions, even though they look like atypical depression, the tricyclics really worked. That’s the line of pharmacological dissection we have been pursuing all along.

JD: It is unfortunate there’s not more of that work.

DK: Who is going to support it? NIMH stopped funding any placebo controlled studies on marketed drugs. The industry is also not interested on a couple of counts. First of all, they prefer, a broad syndrome, because that’s what the FDA approves and you have a much bigger market, so it’s counterproductive from their profit point of view to refine syndromes. So the two major funding sources, industry and NIMH, aren’t going to do
this sort of thing. I have been very fortunate working at the Psychiatric Institute because we have hard line New York State support. Fred Quitkin, Jon Stewart and Pat McGrath have worked with me for twenty-five years or more so we are not at the mercy of the project grant system, which is the pride and joy of NIMH but has this terrible problem. If you don’t get grants, you have to disperse your team. So being able to do long term intensive work becomes impossible.

JD: I’d like to explore a couple of issues since this is a history interview. It’s important to paint the picture of what psychiatry was like when you started to do academic work. I don’t think people appreciate the atmosphere at the university departments of psychiatry dominated by psychoanalysts or the clinical problems in a state hospital with 6000 patients and only 10 doctors.

DK: At the time I went to medical school from 1948 to 1952 I believe every chairman of psychiatry in the United States was a psychoanalyst. In a way, it was understandable; everybody likes to have a theory and nobody was doing much in the way of outcome studies. Psychoanalysis has a charming theory, a lot of literary interests and did something that we can’t claim; it could cure by getting to the root of the matter and resolving the unconscious conflict, compared to the mere symptomatic effects of other psychotherapies and medication, which fostered infantile oral regression. So, it was terrific in terms of promise. The state hospitals were getting bigger and bigger. A deal had been made between the states and the cities. The city was responsible for acute care up to thirty days, and after that it was the state hospitals’ problem. The state hospitals had no after care system and no good treatments. The wards were bedlam; the treatments we had were unmodified ECT, and some people used insulin coma. The prediction was that the expanding hospitals were going to bankrupt the state. The turning point in New York State was 1959; there were 140,000 inpatients at that time. We are down to a couple of thousand now, all due to chlorpromazine. That happened under the title of “deinstitutionalization”; but of course, it wasn’t deinstitutionalization, it was trans-institutionalization, from the state to the city budget. The patients, but not the money, were dumped on the cities, the cities didn’t pick them up and that was a disaster. Instead of an open door we had a revolving door. There was a sudden rise in homelessness. This led to federally supported “community care” which was staffed by therapy minded psychologists. They had a psychiatrist who did little but sign bundles of prescriptions. The ex-hospital patients were not considered appropriate for psychotherapy so the community center clientele were largely non-psychotic. I don’t know if this story is true, but I was told that when Nate
Kline was studying reserpine at Rockland State Hospital, his objective indicator was the decrease in the number of broken windows per week showing patients were getting quieter. Psychoanalysis was still the rage, in terms of both medical schools and psychiatric practice. It promised cure and was the only game in town with a comprehensive clinical theory. I was part of that from 1957 through 1961 as a candidate at the New York Psychoanalytic Institute. I was under the delusion that one could be a research psychoanalyst and that the Institute would welcome this. I quit more than a little disappointed with what happened. I could tell innumerable stories of how counterproductive psychoanalysis has been for psychiatry. One will suffice. When I told my analyst in 1959 that I was going to Hillside Hospital to study drugs in clinical trials, he said, “that is your sadism”, which had not been noticed in the past two years. Descriptive psychiatry was held in very low esteem because it wasn’t important. The underlying conflicts were important and you had to be a trained analyst to perceive them. I was one of the first NIMH Career Mental Health investigators. In 1961, I went to a meeting of about 40 career investigators, and we went around the room saying what we were doing. There was me and one other fellow, who studied whole human beings. We were all in analysis, which was the only way to understand the depths of whole people, everything else was superficial, so budding scientists were driven towards the laboratory. When you were a career investigator in those days, they gave you five thousand a year for your analysis. That was part of my grant but I was so refractory that I quit my analysis before I used the money.

JD: Did you have to give the money back?

DK: I called NIMH and said I’m not in analysis any more, what to do with this five thousand bucks? They said keep it; we’re sure you’ll do something useful with it, which is not quite the situation now.

The other thing we were involved in that has made a big difference is the DSM. I was on the original Task Force that Bob Spitzer put together. At the time it was considered an unimportant effort, so Bob could recruit a bunch of skeptical people. We decided early on that the issue was reliable clinical communication about syndromes. Psychologists had shown that inter-rater diagnostic reliability in psychiatry was dismal. If a patient was called schizophrenic you had no idea what he was like. Symptom description was highly reliable but everybody had their own definitions of diagnosis. This became known as “criterion variance”. That descriptive diagnosis was unimportant was fed by the profusion of contradictory “schools” of etiological theory; Freudian, Jungian, Adlerian, Horneyan, Pavlovian, Cognitive, Behavioral, etc. The DSM-III stand was
that diagnosis should not depend on a particular theoretical presumption, as was the case with DSM-II. This was misleadingly referred to as “atheoretical”. A syndrome was understood as a polythetic category, with inclusion and exclusion criteria and a listing of the symptoms, with a minimum criterion set number. That number was due to clinical consensus alert to both false positives and false negatives while lacking useful systematic data. The text made it clear that these were not carved in stone and clinician judgment was overriding. However, nobody read the text and the residents had to memorize the criteria. DSM-III was basically expert clinical consensus, because we had very little in the way of data. At various times psychoanalytic groups would complain that they were locked out and Bob put a couple of smart analysts on the Task Force but they didn’t have a lot to say and soon left. The real trouble started when we got to neuroses. Many people think that DSM-III was some kind of anti-psychoanalytic cabal but that was not the case. We were trying to figure out how to deal with what was called neurosis. We had good exclusion criteria that neurotics were not hallucinating or delusional, but we didn’t have overall inclusion criteria, apart from theoretical dicta about unconscious conflicts. So we ditched the term “neurosis” and turned to their common descriptive feature as Anxiety Disorders, suggested by Rachel Klein who was a DSM-III consultant. That caused a tremendous wave of resentment and the whole process almost got shut down by the American Psychiatric Association, who thought that we were taking away their bread and butter by saying that neuroses didn’t exist. But we didn’t say that, we said that neurosis was not a useful super-ordinate term. Eventually DSM-III was a totally unexpected, profitable hit. As I remember, Bob Spitzer got the job, after they offered it to Henry Brill who turned it down, saying he wasn’t interested and felt somewhat retired. Spitzer got the job because it was unimportant. The whole notion of diagnosis was just a nuisance and not really central to anybody’s concerns. So, that was a tremendous surprise, although it had its pluses and minuses. It’s been helpful in improving the reliability of clinicians’ descriptive statements. At least, you know pretty well what somebody means when they say a patient is schizophrenic. However, I think it has deflected clinicians away from taking detailed developmental histories because they’ve got those neat symptomatic criteria. DSM-III laid the ground work for arguments about validity and underlying pathophysiology but many, including scientists, made the unwarranted assumption that these clearly heterogeneous syndromes could be handled as if they had a homogeneous etiology. Some think it served to constrict scientists to the DSM-III diagnoses, so if you applied for a grant or for FDA approval you had to use the DSM-III
categories. That may be true but it never bothered me. I came up with atypical depression, panic disorder and childhood asocial schizophrenia because we thought the DSM categories weren’t very good.

JD: From the historical point of view my recollection of academic psychiatry in the 1950s and ’60s was that it was all psychoanalytic, that all mental illness was thought of as a defense against anxiety with only one etiology.

DK: That was exactly what Karl Menninger said. He said that it was all one disease due to more and more anxiety. A psychosis was due to the fact that people had so much anxiety that their ego crumbled and they regressed to the oral stage. So, when chlorpromazine came out it was unanimously mislabeled as a wonderful anti-anxiety agent.

JD: But, not accepted by the analysts. The analysts at that time thought you were not a good therapist if you had to use a medication.

DK: They said it was just a chemical straight jacket. Even among doctors who saw chlorpromazine’s benefit, they thought of it as an anti-anxiety agent, because that was the conventional wisdom. When we applied chlorpromazine to ordinary non-psychotic anxious people, they should have been helped but they got worse, so that didn’t fit. This affirmed my idea of pharmacological dissection; you just couldn’t combine psychoses with anxiety states.

JD: It was all a defense against anxiety. I remember the teacher of psychopharmacology at the University of Maryland said, use chlorpromazine against schizophrenia because that was the severest form of anxiety and use meprobamate against depression, because it wasn’t so severe.

DK: I do not think that was atypical.

JD: Thinking about different drugs for different syndromes was a complete shift in the way of thinking.

DK: Right. People become confused sometimes between pharmacological dissection and pharmacological amalgamation. They think if two conditions both respond to the same drug, it must be the same condition.

JD: No, not necessarily.

DK: Usually you can find substantial differences. It has always struck me as strange and important that every antipsychotic that works in schizophrenia, also works for mania, and often severe depression. It doesn’t work the other way around. There’s something similar and as well as different, concerning the pathophysiology of the major “functional” psychoses. I discussed this in our textbook, but it has been widely ignored.

JD: At the time you discovered panic attack disease it was not known as an entity.

DK: Not at all. It was buried in the anxiety neuroses. In 1895 Freud wrote a paper on distinguishing anxiety neurosis from neurasthenia. It’s one of
the best descriptive papers around. He describes panic attacks exquisitely well, but he doesn’t see it as anything different from all the other forms of anxiety people complain about. People complain about fatigue, belly ache, diarrhea, dizziness, palpitations, etc. Panic is just one of the entities embedded in anxiety neuroses. One of my arguments, which I got into trouble for years ago, with the conventional wisdom is, that panic attack is not fear.

J.D: How do we know that?

DK: Symptomatically, the vast majority of panic disorders that lead to agoraphobia are associated with acute air hunger or dyspnea, which is not a feature of acute fear. That’s been known since World War II by studying people who have been wounded in battle, jumping out of planes or disassembling bombs. They have palpitations, sweating and trembling, but they don’t have acute air hunger. Also, we can experimentally generate panic attacks with IV lactate and carbon dioxide inhalation in the laboratory but only in patients with panic disorder, not in normal subjects or patients with other anxiety disorders or depression. Strangely, there is no increase in output from the hypothalamic pituitary adrenal axis; ACTH, cortisol and catecholamine don’t go up. What is going on? That’s not fear. These features are something different, which led to my “suffocation false alarm “theory”.

J.D: It is interesting the role that Dr. Robbins had when he gave you the freedom to do the work with an open ended mandate.

DK: Lew Robbins was a terrific guy; he was remarkable. He had been clinical director and outpatient manager at the Menninger Clinic for seventeen years but when he approached Karl Menninger and asked to be partner he was told that it was a family business. So Lew came to Hillside intending to make it the Menninger’s of the East, but that was a flop. One reason was because we had two bedded rooms that couldn’t attract the carriage trade.

J.D: Can you make an analogy between your role in that hospital and the role of a specialty clinic in general medicine or surgery? In the modern medical center the hepatology service will see every case of liver disease and the same with any specialty service, so they get a lot of intensive exposure to their area of interest.

DK: That’s right. We also opened up research clinics where we got into outpatient studies. We opened up the first phobia clinic, a depression clinic and a schizophrenic aftercare clinic to do outpatient studies. These were clinics run by scientists as a way to learn things. Of course, clinical services were provided as a wrap around for research.

J.D: In the old days everybody was amalgamated, as in psychoanalysis.
DK: Right.
JD: Which meant that everybody saw everything and all the problems were counter transference.

DK: Right, but the patients also had realistic complaints about the way clinical services were run then. Clinical services now have their own headaches. The nice thing about Hillside was that you saw the patient for a long time, the average length of stay was ten months. The city paid for all indigent care for indefinite stays. That was unusual because the maximum length of stay in any of the city supported hospitals was ninety days. Hillside had a special deal going. When the city finally said it’s got to be cut down to ninety days, this created outrage. The city, using salami tactics, said half your beds can be indefinite, but half must be maximum ninety days. I saw it as an opportunity for a study and Lew Robbins agreed. We took control of the admissions and randomized patients to the different length of stays. As it turned out one group almost uniformly stayed eighty-nine days while the other averaged six months. They were evaluated coming, going out and six months after hospitalization; but length of stay didn’t make any difference.

JD: I want to go on to the follow up of panic attack disease. You alluded to it, but it might be worth a couple more sentences. You had a discreet syndrome with a response to a specific drug so you looked at mechanisms and discovered it could be produced by lactate and CO\textsubscript{2} and maybe a couple of other things. How did you begin to work out the biochemical mechanism?

DK: Let’s take a big step back. Mandel Cohen had shown that in neurocirculatory asthenia blood lactate levels were high. Perhaps lactate was pathogenic. Pete Pitts found, I believe at the suggestion of Eli Robbins, that in what was called anxiety neurosis, intravenous lactate produced anxiety attacks, in a good controlled study. That caused a wave of criticism suggesting that the lactate caused bad feelings; the patients were scared by this until they panicked. Pitts, cleverly, gave the patients EDTA, which is a calcium chelating agent producing tetanic spasms. Despite the patient’s discomfort they didn’t have panic attacks. However this stopped nobody from criticism. To this day, when talking about panic attacks, cognitive behavior therapists assert it’s on the basis of a person being scared of their internal sensations. It makes no sense. Anyway, we started to study lactate when we went to Columbia because we had a good physiological setup, which we didn’t have at Hillside. We expected that the HPA Axis would kick in but we didn’t find that. I went to our Chairman, Ed Sachar, who was a cortisol expert, and showed him our data. His response was, ”What are you doing wrong?” which was
understandable, because people still don’t believe it, although it is very well established now. The next question was, could we block the lactate effect with anti-panic drugs, and it turned out we can. Also, IV lactate doesn’t regularly produce panic in other anxiety or depressive conditions. Drugs often thought to be anti-anxiety like propranolol (Inderal), or intravenous valium (diazepam), don’t block lactate induced panic, so we have something quite specific. One of the theories at that time was that panics were caused by hyperventilation and we did note that during the lactate attack people were hyperventilating, at least they were breathing more deeply. The argument was that when you hyperventilated you blew off metabolically produced carbon dioxide (CO$_2$) ending in a state of acute respiratory alkalosis, and for some reason that nobody quite understood, it caused panic. Therefore, you were supposed to breathe into a paper bag, which brought your CO$_2$ up. Our experimental question was how to get somebody to hyperventilate and not blow off carbon dioxide. We worked out a system where subjects were in a transparent, ventilated, tent at 5% CO$_2$ because there is five percent in the lungs. So they were in dynamic equilibrium, and could not blow CO$_2$. We had a computerized spirograph, so we could measure every breath going in and out. Patients and normal control subjects hyperventilated in room air or in carbon dioxide. Our expectation was that if the hyperventilation theory was correct, the patient should panic when hyperventilating in room air, but should not panic when hyperventilating in carbon dioxide. We found exactly the opposite, which blew everybody’s mind. We were able to convince patients to go through both CO$_2$ challenges and challenges with lactate; showing that the CO$_2$ panic response was a sub-group of lactate panic response. That was odd, because IV lactate produces metabolic alkalosis whereas breathing CO$_2$ causes acute respiratory acidosis. Trying to put that all together was very difficult. And I haven’t mentioned yet the very high incidence of childhood separation anxiety in patients with panic disorder as something else to account for. Then, I went to Washington DC for two years as Senior Science Advisor to ADAMHA, invited by Fred Goodwin. It became a sabbatical, because I didn’t have much to do. Thinking about the whole thing I realized that lactate was a signal of compensation for inadequate glucose oxidation. By shunting pyruvate into lactate, the machinery kept running by anaerobic glycolysis. In the meantime you build up lactate as an oxygen debt. There has been a lot of argument lately about lactate’s role in CNS. There was also evidence that in asphyxiation the first thing that happens to the brain is that lactate goes up. Also, CO$_2$ accumulation is plainly a sign of potential asphyxiation. Further, panic patients had acute air hunger. The way I put it together
was that we have many specific alarm systems, including a potential suffocation alarm system. Following Cannon’s work, people thought of fear and autonomic sympathetic arousal as the sole alarm system for danger. That was usually thought of in terms of predation type danger. However, that we may have different alarm systems keyed to different evolutionary dangers was an idea people didn’t believe. I hypothesized that “spontaneous” panic was due to a suffocation alarm system that differed from the predation alarm system. To diverge for a second, we don’t usually think of thirst and hunger as alarm systems, but they are. But they are slow alarms caused by slowly increasing danger. Deprived of water you get thirsty. You get thirsty and thirstier until finally all you can think about is getting water. It is the same way with food. However with air deprivation the danger quickly mounts so the alarm signal has to be fast because two minutes without oxygen and you are brain damaged.

JD: And predator danger is fast.

DK: Right. And, there are a few other things that have to be fast. Falling has to be fast. Infants have a Moro grasp reflex if dropped six inches. The other way you can get an infant to cry without hurting it is just close its nostrils, no pinching, and they shriek, which may be because their mothers lying on top of them is a recurrent evolutionary danger. Once you get into the framework of multiple alarm systems, a lot of different things in psychopathology begin to resonate.

JD: It’s also interesting from the point of view of social organization. Then, you started some of the first specialty clinics.

DK: Right; and we continue that at the Psychiatric Institute as the only way to learn.

JD: I think a lot of specialties are doing likewise. I mean OCD clinics, Tourettes clinics, so people see more cases and begin to put things together.

DK: That’s correct; otherwise, it’s all bits and pieces.

JD: In trying to work out innovative things you get new ideas and find some of the mechanisms for them. Is the NIMH supportive?

DK: Not particularly. NIMH has gone very basic and, frankly, there appear to be non-clinical review groups for grants. I don’t think anybody on these peer review groups has ever seen an un-medicated schizophrenic. They are primarily researchers at an animal or cellular level. You get a lot of shocking reviews from people who don’t understand that working with humans in clinical trials is not the same as working with rats. I think NIMH is struggling with a narrowly focused peer review system and I don’t know how they are going to correct that, because it has a lot of cachet. I don’t think the RO1 system as presently managed is a good idea because they
are hard to get and any lapse in funding destroys hard to develop teams. I don’t think that NIMH has been supportive of the effort to subdivide syndromes experimentally to detect specific pathophysiologies.

JD: Have you every had a grant rejected because it was too innovative?
DK: I’ve had that happen.
JD: Why did they say it was rejected?
DK: Too ambitious is usually the word they use, or not enough pilot data. It’s a very clumsy situation. Somebody was just telling us the other day that among the people that get career awards only fifty percent go on to an RO1. And, those are the best of the lot. Obviously, there ought to be some changes especially with regard to career building, not just training. This administration is very constricted for money. The next administration may be different. We’ll see.

JD: How close do you think you are getting to the mechanism of panic attack disease?
DK: I think the opioid dysfunction hypothesis is interesting. I’ve got a speculation that there may be a defect at the Δ-opiate receptor level. In our current studies of naloxone anteceding lactate, we’re using doses of naloxone that far exceed the dose for µ-blockade. What I have read is that the µ-knockout mice don’t feel morphine but are otherwise pretty okay. Whereas the Δ-knockout mice are apparently nervous wrecks and might specifically overreact to lactate and CO₂.

JD: If you find the mechanism it would be interesting. You will have discovered the disease, the treatment and the mechanism. What you can say now, which is considerable, is you’ve discovered the disease, the treatment and a number of leads to the mechanism. You have pinned down a good deal.
DK: I think we are a lot closer to a common pathophysiology than to a diffuse etiology.
JD: It’s going in that direction.
DK: I hope so.
JD: I know you have been nominated for the Nobel Prize.
DK: That doesn’t mean a lot. A lot of people get nominated. The Nobel Prize is likely when the scientist is doing the sort of thing that Eric Kandel does; wonderful work, but very basic. That’s what they tend to support.
JD: I hope you get it. I certainly regard your work as Nobel Prize caliber.
DK: Thank you.
RACHEL G. KLEIN

Interviewed by James F. Leckman
Boca Raton, Florida, December 7, 2007

JL: Rachel, it’s a pleasure to have the opportunity to talk with you. I thought I’d just start at the beginning and ask where you were born and how is it that you became so active in the field and have made so many important contributions?

RK: I was born in Paris, France and came to this country when I was fifteen. In college in New York City, I worked in an afterschool community program with underprivileged minority children, and discovered that I had a talent for working with children. My goal, which in retrospect was not a bad one, was to take the children out of the ghetto, and show them that there was a world beyond. I took them to museums, to parks, to all sorts of activities that they had never experienced with their family. I wanted to instill in them the thought that they were part of a larger world.

JL: And, that you really cared about them.

RK: Yes, and it was successful in the sense that they were very happy and appreciative. It was rewarding for me. I had studied comparative literature in college, but based on my positive experience in the after-school program, I decided to do graduate studies in Developmental Psychology, since I was interested in normal children. At the time Developmental Psychology was not well regarded, so I applied to a Clinical Psychology program at Columbia University. I was not thinking of becoming a researcher but went with the expectation of acquiring scientific knowledge about human behavior and development. I was naïve since I had not studied psychology as an undergraduate, and was sadly mistaken. I found there was no body of knowledge, only a lot of theories and beliefs that went unquestioned. Views were expressed without self-criticism, and I was extremely disappointed that I had entered a field that was not even remotely scientific. By luck, I got a job as a research assistant at what was then Hillside Hospital. The way I got the job is not a model of careful career planning. While in graduate school, in 1961, I met Max Pollack, one of the senior researchers at Hillside Hospital, at a resort in the Catskills where I was spending a weekend. He asked me whether I would consider a summer job since the whole research staff, which consisted of Max Fink, Max Pollack and Donald Klein, was going to Munich for the CINP congress, and someone was needed to cover the shop during the summer. There were only two or three such departments in the entire world at the time. It was called the Department of Experimental Psychiatry; we used to joke that the name was an oxymoron.
This was part way through your graduate school experience?

Yes.

You started in the summer and continued to work there over a longer period of time?

That's exactly what happened. I was lucky to be hired on a permanent basis.

While you were continuing your studies, you were also working at the Hillside Hospital?

Yes, and I conducted research for my dissertation there.

What was that on?

It was based on some of Kraepelin's observations about dementia praecox. In graduate school, I had read Kraepelin and was impressed by his clinical reports of different types of psychoses, specifically noting that dementia praecox patients had a childhood history of being peculiar and socially isolated, and that these patients had particularly chronic, unremitting disorders. One of the research projects at Hillside was a prospective longitudinal study of schizophrenic patients who had been discharged several years previously. For my doctoral thesis, I decided to take the opportunity to test Kraepelin's clinical observations. The patients' clinical charts were rich in historical information. Most were young and remained in the hospital for months. Parents would spend days giving information about their offspring. I developed a scale to rate patients in their early childhood and adolescence with an emphasis on social adjustment from the chart material, without knowledge of the patients' longitudinal outcome. Strikingly, some patients were reported to have ordinary childhoods, and others to have been deviant from an early age with peculiar interests and lacking peer relationships.

That was in the record, or something you were judging?

Parents reported that their child never had friends or had befriended another peculiar child, had strange interests, had little interest in socializing with peers and, as a young adolescent, didn't show interest in sex. We found that childhood social history was associated with early onset of schizophrenia, and was a strong predictor of poor outcome. None of the patients with early asocial adjustment had a favorable outcome at any time during the follow-up period; none ever reached independent function. Among those with adequate early histories and relatively later onsets, half did relatively well post-discharge, and the other half did not. The relationship between asocial adjustment and outcome in schizophrenia was markedly curvilinear.

What proportion of individuals fell into that asocial childhood category?
RK: I would have to guess, and I had better not. As my graduate school professor said, you should never quote data, including your own, without checking it!

JL: I apologize!

RK: Not at all. I would guess it was about twenty five percent, and they were mostly males.

JL: This leads me to the next question and it has to do with early mentors you had, people who shaped your career trajectory? I imagine those three people you mentioned played an important role?

RK: That's correct. Max Pollack was a very important mentor; I wrote my very first paper with him. He was a psychologist who was biologically and developmentally oriented, holding that childhood phenomena, especially cognition and brain development, were influential in the evolution of psychopathology. There is all the rage about this now, but it was very unusual at the time. Max Fink and Donald Klein were also important mentors. I spent hours seeing patients with Don during his daily hospital rounds. In the 1960s, graduate training in clinical psychology didn’t include any mention of diagnosis; in fact, it was devalued. Hillside Hospital is where I obtained training in clinical psychiatry. It was at the time when Don was discovering panic disorder and talking about its relationship to early separation anxiety. He also distinguished treatment response to antipsychotics among different types of schizophrenias and he pointed out distinctions between melancholia and atypical depression. It was an incredibly rich intellectual environment. It was also one that was refreshing, having gone through graduate school where we were taught unimpeachable truths. In contrast, the ethos in the research department was that we knew little. I was very impressed with this ability to acknowledge our ignorance.

JL: There’s real wisdom when somebody is willing to acknowledge ignorance and that there’s so much more to learn. Did any of them serve on your dissertation committee, or was it a different group of people?

RK: No, they were not. The members of the committee were psychologists on the faculty of Columbia and other universities. My dissertation was badly received. The study was straightforward in relating that early asocial adjustment was associated with early onset schizophrenia and poor outcome. The rationale for the study was also straightforward in testing a developmental hypothesis about schizophrenia. What caused hostility was that I failed to attribute these developmental abnormalities to the schizophrenogenic parents of the children. As far as the committee was concerned, I had overlooked a major issue by omitting a discussion of the family’s role in the development of schizophrenia. My reply was that
I would be glad to correct the omission if they pointed me to supportive evidence. They couldn’t. Then, I was criticized for the references having too few psychologists and too many psychiatrists.

JL: Shame on you!

RK: Shame on me! I told them I would be delighted to quote psychologists if there were pertinent references by psychologists that I had omitted. There were not. The defense was not a pleasant experience, it felt as if I was on trial and guilty before proven innocent, but I got through it.

JL: And you’ve gone on to a wonderful career. The area of science that you’ve helped to develop and define and seems to originate from that first experience of thinking about diagnostic entities in a more rigorous way, looking in a longitudinal way at what happens to individuals who have certain traits and backgrounds and what may influence their outcome. Is that a correct estimation?

RK: You’re correct, that early experience shifted my thinking and my work.

JL: Tell us about some of the major accomplishments as you look back on your career and look forward to the next phase. Where have your major contributions been?

RK: One doesn’t do clinical research alone. Some of it reflected Don Klein’s interests, especially on separation anxiety. That work led to the introduction of separation anxiety disorder in DSM-III. The diagnosis has stood the test of time as shown by the fact that it has not been altered since. Coincidentally, I had a child with severe separation anxiety, so it resonated. I understood what we were talking about; I lived it, daily, so it was all the more poignant and real. Because of Don’s view that separation anxiety and panic disorders shared some underlying pathophysiology, he hypothesized that imipramine, which worked in panic disorder, would be effective in separation anxiety disorder. We did a study of imipramine in children with separation anxiety which turned out to be very positive. I should add that we did a further study, which was much smaller, where we did not get a drug effect. The patients were much less severe, and it could be a situation akin to that in depression where the severe form is most responsive to antidepressant medication. That’s a testable hypothesis but we never pursued it.

JL: I guess that was your first encounter where you were doing the research with some neuropsychopharmacological agents. Is that correct?

RK: It was my first experience in planning and implementing a psychopharmacology study. However, my first job at Hillside was to evaluate patients who were in an experimental drug study. Patients received chlorpromazine, imipramine, which didn’t yet have a trade name, or a placebo, regardless of diagnosis. I would say this experience was a watershed
for me. When I started I had the typical view among psychologists and many psychiatrists that medication was just a “quick fix”, and that there were much more important interventions that addressed the root causes of psychiatric disorders. This unsubstantiated attitude was shaken by my seeing severely sick agitated and retarded depressed adults who, after six weeks on medication, walked into my office transformed, completely back to their old selves. It was virtually miraculous, and no rational individual could have denied the incredible impact of medication. These observations led me to conclude that one could not simply dismiss the usefulness of psychotropic medication, and there was great merit in learning more about its value.

JL: It reminds me of that era of large state hospitals, where people were institutionalized for long periods of time and lived there and how transforming it must have been to see people revert within six weeks to someone who had been lost.

RK: These are unforgettable experiences that mark you.

JL: I’ve encountered your work with regard to anxiety disorders and in terms of hyperactivity and ADHD. I’ll ask you to teach us about what you’ve learned in those two areas, and you can take your pick about which you want to start with.

RK: I would like to start with ADHD, which we began studying in the late 1960’s. The impetus for doing it was the disbelief about reports of stimulant efficacy in children with behavior problems. I had to see for myself. Between 1970 and 1978 we ran a research clinic for children we now diagnose as ADHD. The DSM-III description of ADHD was, in large part, based on the cohort of children we saw at that time. They were the defining group due of the approach the DSM-III applied to consider new diagnoses as candidates for the nomenclature. One had to produce detailed clinical descriptions of illustrative cases. Since we were conducting systematic studies, we had an ample supply of very well documented clinical cases.

JL: Did you advertise the clinic? How did people learn about it?

RK: At the time, outpatient treatment resources were very limited and consisted mostly of child guidance type services. There was a great unmet need and few competing treatment centers for children with behavior problems. Our only outreach effort for referrals was to inform local schools of our services. We also invited guidance counselors for group meetings to identify their needs for professional services, and to form relationships with them. Our rule was that a child had to be referred by a school. This was due to the controversy about identifying exuberant children as hyperactive, and the negative perception of treating behavior with
medication. There was a great deal of public opinion about what was considered the “medicalization” of behavior. A common argument was that parents were intolerant and not accommodating to their child’s normal rowdy behavior. By requiring that children have serious adjustment problems in school, we wished to avoid treating children whose difficulties were not pervasive, or did not affect all or most significant functional domains. Thus, children had to have behavior problems at home and school; we did not want to treat children whose parents alone, or teachers alone, saw them as in difficulty. In addition, the research team led by Don put great stock in considering a person’s history in the diagnostic process. So, we also required that children have a history of behavioral problems. We knew very little about hyperactive children, and we wanted to ensure that we treated true cases by requiring that the children’s significant adults confirm that the child had serious problems, and that these were not of recent origin. At the time, stimulants were rarely used in outpatient centers, and never by pediatricians. As a result, most of the children we saw had never been treated with medication, or received any care for that matter. It would be very difficult now to recruit a large number of children with ADHD who had no previous exposure to any treatment.

JL: Did you have in mind, from the beginning, that you would be following some of these individuals into adulthood?

RK: Yes, we did. In fact that was an argument we made in our early grants, pointing to the potential for follow-ups to provide information that could validate the disorder. We knew that if the disorder did not predict a specific course, it was unlikely to be meaningful. In addition to providing such knowledge, it behooved us to be able to tell parents what they could expect later on. It’s very problematic to have a child who’s in great difficulty and not know the likelihood of the child improving versus continuing to have problems. So, knowledge of course seemed important on several levels. Don’t forget, we had done longitudinal studies of schizophrenic patients, and appreciated how valuable that experience had been. We collected data at referral that would make a follow up study possible and allow the examination of clinical predictors of course.

JL: If I came to you with my child, you did your assessment and determined that this was a child with ADHD, what could you tell me about what the likely outcome for that child and the important variables that might influence that outcome?

RK: How old is the child?

JL: Let’s say the child is ten years old.

RK: The child, I assume, is a boy?
JL: Yes, it’s a boy and he’s been handful for years and we keep getting complaints from school, in terms of his behavior. He seems very impulsive; although, he’s quite bright and can focus his attention on things that he’s interested in. What could you tell me about what to expect in the future?

RK: Well, I’m not always as candid as I should be with parents, because I am reluctant to cause worry that may not be justified.

JL: Pretend I’m not a parent and you’re just teaching me.

RK: I can try to speak to you as a parent. I would say to watch out for adolescence since it’s a high risk and challenging period of development, especially for boys, and for boys with ADHD. If the child never had serious antisocial behavior, I would reassure the parent that the child has a very good chance of managing well, especially if the child were bright. I would tell parents that they have to be prepared to accommodate him in school to optimize the child’s experience. It’s not helpful to push the child to adapt to circumstances that he cannot cope with adequately since it is likely to lead to demoralization. I would encourage parents to make it possible for him to find success in school. Should that be impossible, they will have to protect him from being tempted into rule breaking behaviours. I would emphasize that this is especially important since it may lead to substance abuse, and then dependence. If so, you’re on a slippery downward slope. But, if the child does not develop antisocial behavior and if he’s followed and well treated, he has every chance of doing well.

JL: What role will psychopharmacological agents play in the unfolding of that story? Are they a critical element, in terms of insuring the success of that child, or it’s still something that we’re not certain about?

RK: I’m relatively pessimistic about the likelihood that medication can prevent the evolution of a disorder. I don’t think the evidence is very good for that. In psychiatry in general, we don’t have good models for disrupting the natural history of a disorder. But if the child continues to be treated and to respond to treatment, he will have that much more opportunity to succeed. It’s not so much that you’re preventing the illness, but one may be preventing secondary complications that frequently occur if the illness is not treated. I’m afraid that we cannot represent treatment as a preventive measure with confidence.

JL: You’ve also written about learning disabilities with regard to ADHD. What role do they play in determining what the long-term outcome will be?

RK: It depends on what aspect of outcome we focus on. In terms of the actual symptoms of ADHD, or complications of ADHD, learning disabilities made no difference; however, not surprisingly, they mattered for academic attainment.
JL: What haven’t we touched on with regard to some of the major findings; when I think of you I think of that longitudinal study and the dedication that you and those families must have made to the success of that project to carry it forward for so many years.

RK: At the time, it was assumed that ADHD was a developmental disorder, in the sense that it disappeared in adolescence. The first surprise was that most boys worsened during adolescence, although about a quarter no longer had the disorder by the time they reached the age of 18. We had been careful to exclude children with conduct disorder because, based on Lee Robins’ work, we thought that conduct disorder and ADHD, as it is now called, were different conditions. Yet, a substantial proportion of the children developed antisocial behavior, and conduct disorder/antisocial personality disorder de novo during adolescence. Also unexpected was the finding that the development of conduct disorder was completely accounted for by individuals who had retained ADHD. We were the first to report an excess of substance abuse and dependence in adolescence. This was not an independent outcome; rather, it was a complication of having developed antisocial personality disorder. Thus, we found a cascading developmental trajectory. The maintenance of ADHD was linked to the development of antisocial disorders which in turn was followed by substance use disorders. One of the things that surprised us is that, even though we had excluded children who had conduct problems, who had a pattern of lying, truanting or stealing, etc., there were still some individuals who had mild or transient forms of some of these behaviors. What we found was that even a small dose of rule breaking behavior was a negative predictor of outcome. Therefore, I think it is terribly important to appreciate that treatment needs to be maintained over extended periods of time, that clinicians inquire about any conduct problems, and not dismiss them but rather focus on preventing them. In sum, we found a highly specific pattern of long-term psychopathology, which we thought validated the diagnosis. We did not find an excess of anxiety or mood disorders. But others have reported different outcomes, finding elevated rates of a wide variety of disorders. It is difficult to reconcile such disparate findings.

JL: You didn’t see that many presenting later on with, what we now know as pediatric bipolar disorder and things of that sort?

RK: We did not find any bipolar disorder in our group. On the other hand we excluded children with conduct disorder, so those may be the ones that might be more likely to become bipolar. I understand that adults with bipolar disorder report childhood histories of ADHD. That may be correct. However, if bipolar disorder has a population prevalence of about 1%,
and only a minority of these report having had ADHD, we would need huge samples, in the tens of thousands, to find a relationship between childhood ADHD and adult bipolar disorder. By the way, we are now evaluating these children at the age of forty. Out of over 150 subjects, there are two individuals who became psychotic in their thirties, and none among the controls. It is very difficult to come to some clear prognostic statement about a rare outcome. However, it is possible that in a study of adults with late onset psychosis, one would find a large proportion with childhood ADHD.

JL: I’m delighted we’re going to hear more about that cohort, because it’s been such an important one to follow, in terms of our understanding of the condition. We’ve talked a bit about Panic and Separation Anxiety; I see you as having made really important contributions to our nosology and our understanding of those conditions. Would you share a little bit about what you think are the most important findings there and the next steps that we need to take to advance our knowledge?

RK: In terms of the nosology, the work we did with Separation Anxiety was the basis for introducing Separation Anxiety disorder in DSM-III. The DSM-II contained the diagnosis of Phobic disorder for children, which encompassed all childhood anxiety. The DSM-III was the first attempt to distinguish various forms of childhood anxiety disorders. The diagnostic shift was seminal in the sense that it fostered biological studies of children with Separation Anxiety and studies of neural pathways in different child anxiety disorders. Correlates of Separation Anxiety have been noted; specifically, from the work of Daniel Pine, we found CO$_2$ hypersensitivity in children with Separation Anxiety disorder and, more recently, we have found that, among children with Separation Anxiety disorder, parental history of Panic disorder influenced CO$_2$ hypersensitivity. Even within Separation Anxiety, there is heterogeneity and perhaps one way to subdivide the group is through parental history. For future studies, it may be useful to make that distinction. In terms of the nosology, I already mentioned that our early studies with children who had what was called Hyperkinetic Reaction of childhood were very influential in DSM-III. They helped specify excessive motor activity, impulsivity and inattention as key features of the disorder. That was changed in the DSM-IIIIR. We don’t need to go into the reasons why, our work had nothing to do with it, but the DSM-IV went back to the DSM-III approach for the diagnosis of ADHD.

JL: Are you fairly content with where we stand currently with our nosology, with regard to these conditions, or would there need to be further refinements in DSM-V?
RK: This is a very personal view. I’m a little disappointed; I should say more than a little, in how the DSM is used. We had great hopes that it would alter our approach to patients. It has not fulfilled its promise. The document is not to be faulted; rather, the field is. We have adopted a check list approach to diagnosis, and the sense of what has gone wrong has become lost. The concept of Separation Anxiety is not whether the child does or does not do A, B, C, D, which may be important, but it does not tell the whole story. Rather than identifying the functional construct underlying the condition, it has become a numbers game. The same applies to ADHD. There is a host of papers reporting on individuals who do not meet the stipulated number of criteria for a diagnosis, but who are impaired. The DSM was never intended to be a formula or rule. It was to be a guide for clinical purposes. Obviously, for research, one must adopt a uniform standard for diagnosing subjects, but the DSM was not meant to be a research tool exclusively.

JL: I hope that your comments are ones that many people will hear in their training. We’ve talked a little bit about some of the individuals who were important mentors to you in your life and you mentioned one individual for whom you have provided mentorship, Dr. Daniel Pine. Are there other trainees you’d like to just tell us about and share some things about the experience of being a mentor?

RK: I must confess I never thought of myself as a mentor, but as working with young people with shared interests. I can mention Harold Koplewicz, who is now the Chair of the Department of Child and Adolescent Psychiatry at New York University. He was a Research Fellow with me, which was a rewarding experience. Believe it or not, John Kane worked with us in our work on the hyperactive children, so I like to think that this experience had something to do with his decision of entering research. There were people that we hired to help us in the studies, who went on to be independent investigators, through that collaboration. One of them, in terms of ADHD, is Howard Abikoff, at NYU, who has gone on to work very actively. He was our first observer on classroom behavior of ADHD children. Jeffrey Halperin, now at Mount Sinai, also went on to conduct independent work in ADHD. Prior to working with me, neither of them had any interest in, or knowledge of the disorder. Laurie Miller, who was interested in aggression, was inspired to go work in prevention. She is now running a multi million dollar program for Prevention of Conduct Disorder.

JL: And, what is the name of her program?

RK: Parent Core. It consists of training minority parents to teach other minority parents in their community. There are others I work with now who are on their way to becoming dedicated researchers in child psychiatry.
JL: You might mention a name or two for the record.

RK: Carrie Masia Warner who specializes in the treatment of anxiety disorders, and Vilma Gabbay, in the neurobiology of adolescent depression.

JL: They ask us about the role that you’ve played in writing and editing books and journals. They want some record of what contributions you’ve made in that way. There’s another very interesting set of questions about the interface of family life. We have already learned some things in terms of your spouse and one of your children. Maybe, we could ask which books you’ve published are your favorites, or the one that you’d like us to draw our attention to.

RK: My favorite is old; I don’t think anybody looks at it any more, and that’s always disappointing. It’s called Diagnosis and Drug Treatment of Psychiatric Disorders, which was published in 1980. Donald Klein is the senior author. It was a joint effort with him, Fred Quitkin, Arthur Rifkin and me. It reviewed the extant literature, which was a doable task then. It would be very difficult now. It also included practical clinical information about differential diagnosis and psychopharmacological treatment, and discussions by Don, which are still relevant, on principles of classification.

JL: Wow, the entire literature! My goodness, that’s an ambitious task. And can you just tell us a few of the honors that you’ve received over the years? They do ask this question, and I don’t mean to embarrass you.

RK: Do I have to answer it?

JL: Please do; people will want to know.

RK: I received a Merit Award from NIMH and the NARSAD Ruane prize in Child and Adolescent Psychiatry, which you also received this year. There are others but I am still very active in my field of research and much more interested in what may lie ahead than in any past accomplishments.

JL: Well thank you Rachel that seems a most appropriate way to conclude our interview.
TB: This will be an interview with Conan Kornetsky for the ACNP archives. I’m Thomas Ban. Tell us where and when you were born and how you moved into the field.

CK: I was born in Portland, Maine on February 9, 1926, the third child of Alex and Ida Kornetsky. My siblings were a sister, 12 years older and a brother 14 years older. Due to an error by the obstetrician my mother died a week after my birth. During the first year of my life we lived in a large three family house with the families of my mother’s two sisters. After a year my father gathered up our family and moved to Chelsea, a suburb of Boston. Because he could not take care of me and work I was boarded out to another family. After two years my father remarried and we were all together once more. This lasted for a couple of years before my stepmother died of cancer when I was in kindergarten. From that time until I finished third grade I was a “latch key child.” During those years, during the depression, we moved every year around Boston because landlords would give you 12 months to live in an apartment for 11 months rent; moving was a great savings. I did kindergarten through third grade in the Boston area; my sister graduated from high school and my brother from the Massachusetts school of optometry. But, my father could not find work in the Boston area. My sister went to live with one aunt in Portland, I with an aunt and uncle who had no children. My brother took a job in northern Maine with an optometrist and my father found a job in a shoe factory in Auburn, Maine. I stayed with my aunt and uncle through high school. Although they tried their best I was not a happy child. They correctly saw me as difficult. I loved to read, but was not a good student. I was fairly independent. I loved history, mathematics and science but I didn’t do well in those subjects. I used to argue with the teachers and if you disagreed with the teachers, you were thrown out of the classroom and had to spend time in the principal’s or Sub-Master’s office. The Sub-Master and I became very friendly; he used to get me back in the classroom and worked out some apology with the teacher.

TB: When did you graduate?

CK: I graduated high school in 1943 and entered the University of Maine in engineering in June. World War II was on so I tried to get time in college before I went into the service.

TB: How old were you when you graduated?
CK: I was seventeen years old and did one year of college by January 1944. Then I was inducted into the US Army, Air Force in March. I was supposed to train as a navigator but due to cutbacks they gave me temporary training as an engineer on B24 bombers while I was waiting to be trained as a pilot or a navigator. When the war ended, they gave me a choice of early discharge or pilot training with three additional years in the service. I decided that was not a good choice, so I was discharged.

TB: When were you discharged?

CK: In December, 1945 and I went back to the University of Maine in January, 1946. I decided I didn’t want to be an engineer, so I went into a liberal arts program and decided to look into various fields. I took a lot of philosophy, history, and psychology, found psychology and philosophy the most interesting and received my degree in psychology in 1948. I had a number of interviews but couldn’t find any job that was satisfactory. At that time the GI Bill would pay for further education; first I thought I would go to graduate school in philosophy. Then I decided I would not be able to earn a living if I did that, so as a second choice I thought clinical psychology would be interesting. I had taken an intensive course in testing that certified me as a mental tester. I had also taken a course in abnormal psychology in which we visited a local state hospital a number of times where patients with different diagnoses were presented. So I looked into the American Psychological Association’s listing of approved schools for clinical psychology.

TB: What did you find?

CK: The only school approved in New England was Yale. Approved schools elsewhere were all first rate but I was not that good a student; I had a mixed academic record in college. I did very well in courses I liked but in courses I didn’t like I didn’t care what grade I got. Also, I was very active politically after the war. I was a member of the American Veterans Committee, which was a radical leftist group. I was more interested in politics than grades. I had a professor of philosophy and religion and we used to go to a local pub and argue. His aim was to prove that God existed and my aim was to prove God did not exist. Every paper I wrote for him was to prove that. We had a great relationship and he said, “See if the University of Kentucky is an approved school”. He used to teach there and wrote me a good recommendation. So I applied and with his recommendation I was admitted into the clinical psychology program.

TB: When was that?

CK: I arrived in September, 1948. I had the GI Bill but after a few weeks I wanted to find an additional source of funding. The GI Bill paid for books and tuition, plus a stipend. I got a job in a sorority house as a house-boy,
a glorified janitor. But then the Chairman of the Department told me there was an opening for one student in the Clinical Psychology Department at the US Public Health Hospital in Lexington, Kentucky. This was a hospital for the treatment of drug addicts. At that time I did not know what a drug addict was and the only drug I knew about was alcohol. I didn’t know anyone who used marijuana. However I had to make a choice, sorority house or a mental tester; so I took the job as tester. The stipend was board, room and laundry, so I would live at the hospital. The Lexington USPHS Hospital was also a prison for the incarceration of addicts. It was a great experience living there. My room was a cell similar to the cells of the prisoner-patients. The only difference was that I had a key to my cell. I didn’t have a car, but transportation was fine. It was five miles from the University. There was no trouble getting back and forth during the day, but in the evening I was stuck there, so I used to study and hang around and chat with the prisoners who would tell me all about drug use.

TB: That had to be interesting.
CK: I found the most interesting place to hang out was the research ward. I spent time talking to the patients and learned what experiments they were on. I was learning a lot; I don’t know if I believed all the stories, but they were interesting. The director of research was Harris Isbell. He would make rounds every evening and he kept seeing me there. After he learned who I was he would tell me about the experiments including a new clinical experiment that he was planning on chronic barbiturate intoxication.

TB: This was what year?
CK: The fall of 1948. At that time it was not known there was physical dependence to barbiturates. They knew there were sometimes convulsions and seizures, but no one had ever demonstrated if that was withdrawal or intoxication. So he was planning to do a study. Because he had no psychologist he asked me if I would be willing to participate. My main job was that every afternoon, I would do three Wechselr IQ tests on patients and write them up. I still had to do that, but I started to participate in the study. This was pretty heavy stuff for a first year graduate student. I knew IQ testing and a few new tests that I was picking up in graduate school. As a first year student I was pretty skilled in IQ testing. I developed further one of the sub-tests on the Wechsler so we could use it repeatedly. It was the Digit Symbol Substitution Test. What I did was to change the code every time they took the test. Although there would be a practice effect, there was no learning of the number-symbol code. I probably broke all sorts of copyright laws. I also used projective tests that I was learning to use that were popular. There was
a resident in psychiatry participating and Dr. Isbell, a technician and myself. I was basically the third professional, the psychologist on the project, which was great.

TB: It was your first professional experience in research?
CK: That was my first professional experience as a researcher. I spent most of that year participating in the experiment and writing my results. During that year I learned a great deal about the behavioral and pharmacological effects of addicting drugs. One of the missions of the Research Department was to test new drugs for addiction liability and physical dependence, as well as analgesic potency. They never found one, but that was the mission. Nathan Eddy from the National Research Council would come periodically with a bag full of new drugs to try on patients. These were prisoner patients who would volunteer. They would be given drugs under controlled conditions and were followed very closely to determine if physical dependence developed.

TB: How many subjects were included in a typical experiment?
CK: There were a few subjects in each experiment. There were six in the barbiturate experiment. One of them quit. What we found was that besides continuous intoxication, during abrupt withdrawal from daily administration, all the subjects had convulsions or a psychosis. That was the first demonstration there was physical dependence to barbiturates and it was the first publication with my name on it: Isbell, Altschul, Kornetsky, Eisenman, Flanary and Fraser in the *Archives of Neurology and Psychiatry*, 1950. Isbell urged me to write a separate paper giving more details of my results. I did, turning in a hand-written manuscript of about a hundred pages. Well, my section covers two published pages in the original paper. Isbell was very kind; he taught me how to whittle it down and it was published as a separate paper. He insisted that for my career it was better if I will be the only author. The title of the paper was; *Psychological Effects of Chronic Barbiturate Intoxication*. It was published also in the *Archives of Neurology and Psychiatry*, in 1951. It was all heady stuff for me.

In June of 1949 I was married to Marcia Smargon in Boston. Marcia and I were classmates at the University of Maine. During the academic year 1948-1949 she was a graduate student in social work at Boston University. By time I returned to Lexington with my bride Abe Wikler had returned from his year long sabbatical. Because the stipend of board, room and laundry was no longer applicable now that I was married, Harris Isbell hired me as a technician from money he didn’t need for an animal caretaker. So I would be paid from now on as a technician and was hoping that I wouldn’t have to do anymore IQ testing.

TB: So you had enough from IQ testing?
CK: I was getting disenchanted. One of the things I was trying to do was psychotherapy but I found I didn’t like it. I found it interesting at first, but by the third time I saw a patient, I was bored. My wife still didn’t have her degree but she got a job in the child guidance clinic as a social worker with the professor of clinical psychology. This was probably good for me. My first contact with Wikler did not create the impression I would have liked. Although Dr. Wikler had been back from sabbatical for only a couple of weeks he had already started experiments in which he measured autonomic responses and reflexes in dogs after drug administration. These were recorded on smoked kymograph paper stretched between two “drums”. A stylus operated through changes in air pressure that would move the stylus back and forth on the smoked paper. He would later shellac the paper to make a permanent record. In the course of this process these paper loops were hung on pegs outside his office and until they were shellacked they were vulnerable. I came bouncing into his laboratory to meet the famous Abe and when I inadvertently brushed against some of the smoked paper loops, I heard a scream from Abe, “who the hell is this stupid ass”? That was my first contact with Abe, who later became my close friend, mentor and colleague. After he realized who I was and that I wasn’t stupid, we became very close friends. Another person came on the research staff in the summer of 1949, a psychologist named Harris Hill. Isbell assigned me to work with Harris Hill and we did some early studies on anxiety, analgesia and morphine. Abe would run an informal morning seminar. So every morning we would meet over coffee and he would give the seminar. We would have discussion groups deciding on experiments; that is where I proposed what I thought was the greatest experiment in the world. It was probably the proposal I’m most proud of because it was a very early demonstration that environmental factors could affect the way a drug acted. What I proposed was a simple reaction time study in which we would change the motivation of the subject during the reaction time. The hypothesis was that changing the motivation of the subject would alter the way morphine would act on reaction time. I proposed this and Abe had a way of quizzically looking at you and the more he looked the more stupid you felt. Finally, Abe was very direct and said it was a stupid idea. The master had spoken, but a week later he bumped into me in the corridor and said it was a great idea; but we had to change it a bit. We did the experiment and it turned out as I predicted. In the presence of anxiety precipitated by a situation in which the subject did not know whether he would receive the punishing electric shock until the “go” light appeared, behavior became disorganized and reaction time was slowed. That led to a series of experiments in which we
measured pain threshold under different environmental conditions, with and without morphine. I spent three years doing those experiments with Abe and Harris Hill. My dissertation was on the effect of morphine and the role of environmental factors on the perception of pain.

TB: What did you use for producing pain?
CK: Radiant heat on the forehead and I measured pain threshold using classical psychophysical means, which hadn’t been done before.

TB: So you studied the interaction of environmental factors and morphine on the perception of pain?
CK: By manipulating the environment just prior to the experiment. Basically it consisted of establishing rapport with the subject by spending about fifteen minutes prior to the experiment in friendly conversation. We did a whole series of experiments, but mine were unique because I measured autonomic responses, verbal reports, and used classic psychophysical means. That was my PhD dissertation. Abe was the director of that dissertation but because he did not have a faculty appointment at the time, he was not the one who signed off on the thesis.

TB: When did you get your degree?
CK: In 1952, and then I moved on. At the time I was doing my dissertation I was involved in other experiments. There was a big increase in juvenile drug addiction and a young psychiatrist, Donald Gerard, came to Lexington. He and I were assigned to study juvenile drug addicts. We did for about a year and a half. Then it was decided we had to do a follow-up study in a large urban area and we picked New York. So in the fall we moved to New York and we studied juvenile addicts in 1952 and 1953. We probably did the first controlled study of juvenile addicts; it was interesting because our control group consisted of friends of addicts. The big problem we had was finding friends who were not addicts themselves. It took us a year to get 22 “friends”.

As Dr. Gerard and I were the so called experts on drug addiction, having been at Lexington, we were asked to help Dr. Isidore Chein, in the Department of Social Relations at NYU, to get started on a big NIMH sponsored study of juvenile addiction that led to the book, The Road to H. Don Gerard, after our year of study of the friends of juvenile drug addicts took a position with Chein and was one of the co-authors of the book. That is probably the best social psychological study of juvenile addiction in a large urban area. The book starts out with the sentence; “H is for Heaven, H is for Hell, H is for Heroin”. During my last year at the Lexington Hospital my status changed. At that time I was an officer in the US Army reserves and when the Korean War started I was called to active duty in 1944-1945. Because I was not eager to go into the Army again,
Harris Isbell had me transferred from the Army to the USPHS commissioned corps which was still part of the armed forces, a hold over from WWII.

TB: What did you do after the completion of the juvenile addiction study in New York?

CK: At the completion of the juvenile addiction study I was asked to spend another year in New York to study LSD with Murray Jarvik at Mt. Sinai Hospital and with Harold Abramson at Long Island Biologic Laboratory. Then, in 1954, I moved to NIMH in the intramural program at Bethesda. I was there from 1954 to 1959 in Seymour Kety’s Laboratory of Clinical Science. In the laboratory next to mine was Julius Axelrod. In fact I needed some temporary lab space at one time, and Julie had a little space he allowed me to use. Anyway, I did a series of studies on the effects of psychoactive drugs on performance. First, I studied the effects of chlorpromazine, analgesics, barbiturates, and opiates in humans. I also did sleep deprivation studies. Some of those I did with Alan Mirsky. He and I developed a hyper-arousal theory of schizophrenia, namely that the schizophrenic was in a state of hyper-arousal and not hypo-arousal due to a filtering problem. The idea came from studies performed in the mid 1950s to the 1970s, working with the Continuous Performance Test (CPT) in which I found that amphetamine did not improve performance of subjects who were functioning at full capacity. Their performance was actually impaired by amphetamine.

TB: Could you tell us something about the CPT?

CK: The CPT was a straight vigilance task. Random series of letters were presented on a screen at a constant rate and the subject was required to press a simple lever whenever an X appeared. You could make it more difficult, by requiring pressing the lever for the X only if it follows an A. During the 1950’s the only effective drug for the treatment of schizophrenia was chlorpromazine. We found that chlorpromazine would impair performance on the CPT, but not on the DSST. We would then compare the findings with chlorpromazine with the effects of a barbiturate. Barbiturate produced no impairment on the CPT, but a clear impairment on the DSST. It was a clear dissociation between these two tests in normal subjects. We then went on to study schizophrenic subjects. We found that schizophrenic subjects performed as well as normal subjects on the DSST but were markedly impaired on the test of attention, the CPT. Mirsky and I were lucky at that time because the schizophrenics we studied had not been chronically receiving neuroleptics

TB: Didn’t you do some studies with amphetamine in schizophrenics?
Much of the work I did with amphetamines in schizophrenics was after I came to Boston University in 1959. During this period I administered single doses of d-amphetamine to chronic schizophrenics and I did not see any exacerbation of symptoms. I started measuring blood pressure effects and I kept pushing the dose up and finally at 40 mg of amphetamine, I had to stop because of increased blood pressure. There were no other effects. Our CPT studies with Alan Mirsky had already demonstrated that a major deficit seen in schizophrenics was the trouble of focusing and filtering stimuli. Since in normal subjects amphetamine allows you to filter and focus, I thought it might improve behavior in schizophrenics. So I proposed, at Medfield State Hospital, an experiment in which I would chronically administer amphetamine. Harry Freeman, Director of Research, was all for that study. However, the committee that was equivalent to present IRBs was not enthusiastic. They said I would have to do a pilot study before they would give permission for a more elaborate study. They allowed the administration of 20 milligram of oral d-amphetamines to the subjects in the evening. Although they predicted that the patients would be climbing the walls, they gave permission for one week with a cross-over to placebo for the second week. Half the subjects received the amphetamine the first week and a placebo the second week. It was reversed for the other half of the subjects. Although we were interested in sleep behavior we did not have the facilities to monitor sleep. We had the nurses, on the hour observe each subject and score them with a plus (+) if they appeared to be sleeping and with a minus (-) if they appeared not to be sleeping. I did not want the nurses to ask if they were sleeping. One of the subjects quit, so I was left with 9 subjects. Compared to placebo there was no difference between the treatments. With amphetamine 3 subjects looked like they were sleeping more, 3 looked like they were sleeping less, and 3 showed no change. They certainly did not exhibit a potentiation of their schizophrenic symptoms or exhibit excitation from the amphetamine. The nurses reported no difference in behavior when the subjects were administered amphetamine. Whether they had shown any cognitive or other improvement I don’t know.

In 1970 when I presented these data nobody paid attention to it. I asked Danny Freedman, who was the editor of the Archives of General Psychiatry, if he was interested in publishing this paper, so in 1978 the paper was published with the title Hyporesponsivity of Chronic Schizophrenic Patients to Dextroamphetamine. As before, nobody paid attention to it. Getting back to chlorpromazine, my question was how could schizophrenics got better if the drug decreased...
arousal that would impair normal people. Allan Mirsky and I postulated an inverted U hypothesis of arousal so that where you are on that curve determines your response to amphetamine. We plot along the abscissa the arousal level, and if the normal person is on the ascending side of the inverted U and you administer amphetamine it results in an increase in arousal. If the person is on the descending side of the U, over-arousal, then amphetamine would move him further on the descending side and cause a decrease in arousal. Thus amphetamine has the same basic pharmacological effect in normal subjects and schizophrenics, moving both to the right, increased arousal; however, the actual response depends whether you are on the ascending or descending leg of the inverted U. If you are on the left side of the peak, and you are given a drug, you become impaired. Since schizophrenics are over the hump, if you give them a drug they do better. Now that is an over simplification. But our belief was that there are some schizophrenics who are like that; and that there is a filtering problem. I did a number of studies with Marissa Orzack in the 1960s, and showed that some first-degree relatives of schizophrenics responded in the same way as some schizophrenic patients. The nicest study was that of Gerry Wholberg. He was a psychiatrist and a research fellow at Boston University. The question he asked was whether our findings are dependent on a state or a trait. So he took patients on medication and in good remission, and gave them the CPT test. First, he did not find any impairment on the CPT. Then he decided to do the test in a situation in which the patients were distracted by a noise. He did this in schizophrenics in good remission and with normal subjects after he did a recorded interview. He found that schizophrenic patients, exposed to an interfering noise, did not do well on the test. They were holding jobs, functioning people out in the world in good remission, yet they showed impairment when he added the noise because they couldn’t filter well. I thought that was a fantastic study. Yet for some reason, nobody paid much attention to the findings. I believe because it did not fit with the main stream of thinking at the time.

TB: Did Gerry Wholberg follow up his findings?
CK: Gerry left and took a job as Director of Clinical Training at Boston State Hospital when one of his residents saw a paranoid patient who left against medical advice. The patient returned and wanted to see the resident. When the patient was alone with the resident he pulled a gun out of his pocket and pointed at him. They were in a room with a small window in the door. When a nurse saw the gun she called Gerry. Gerry felt responsible because it was his resident and went in the room. He talked for three hours with the patient. Finally, when he thought the patient was about to
give up the gun, the patient pulled the trigger. The bullet hit him in the head. He lingered for a month before he died.

TB: Why didn’t you follow it up?
CK: I was having trouble getting funded for my schizophrenia research. They just weren’t funding it so I focused on the drug abuse. I was mainly interested in tolerance and did a lot of work with Joe Cochin, on single dose tolerance. Our argument was, once you experience a drug, there is going to be some residual tolerance. There was a study done when I was in Lexington by Frank Frazier, in which he found that drug addicts, six months after their last dose, show tolerance to a single dose of morphine. He needed normal volunteers for his study, so I volunteered and as a subject received a single dose of 20 mg of morphine intramuscularly. I must admit that I got a high on it. I really liked it. However, I didn’t want to try it again because I didn’t like the loss of control.

TB: Would you like to say something about your recent research?
CK: I’m interested in two things, aging and opiates and have been working in these two areas for two years now. I’m working on the effects of analgesics on the reward system in aging. The general belief is that older people need less morphine to produce the same analgesic effect. I don’t believe that, and my findings are in the opposite direction. I have a small grant to do preliminary work; that is coming to an end and I am writing grants to do more in this area. I am very interested in this research. I think research with analgesics is very important and I also think older people are undermedicated. I’m also working with alcohol. I am still active.

TB: What would you like to see happen in your area of research in the future?
CK: As I grow older I am bothered by some of the things I hear. I would like to see more attention paid to science and less to money. What is driving science now is not the excitement, but something else and that is bothersome. I get excited when I see something new. I love it when the students get excited looking at data.

TB: On this note we should conclude this interview with Dr. Conan Kornetsky. Thank you, Conan for sharing this information with us.
CK: I enjoyed it. Thank you, Tom.
JEROME LEVINE
Interviewed by William T. Carpenter, Jr.
Boca Raton, Florida, December 12, 2007

WC: This will be an interview with Jerome Levine for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College, in Boca Raton, Florida. I am Will Carpenter. I would like to hear about your life and how you see the field progressing. Tell us about your early experiences, your education and how you moved into the field?

JL: I think that this is a terrific idea. We are at a point in time where we can still capture the whole history of modern psychopharmacology. I was born in New York City in 1934. I grew up in New York and on Long Island until I was about eleven years old. Right after the Second World War, in 1946, my parents decided to move to Buffalo, New York where we had relatives who they went into business with. I went to school in Buffalo, graduated from elementary school and onto high school at the time of the Korean War. Because of the war they were pushing people through school a bit faster, so I was able to leave high school before I graduated. No one in my family had ever gone to college so I didn’t know how to approach things, but I knew there was the University of Buffalo on Main Street up from my high school. I applied and started undergraduate school in 1951. I had always been interested in science and chemistry and my mother used to holler at me for doing experiments in the basement with my chemistry set. I started as chemistry major, but had to take some other courses in order to qualify for the BA degree. I started taking some psychology courses and liked it as much as chemistry. There were some excellent psychologists at Buffalo and I wound up a double major in psychology and in chemistry. As I was coming to the end of the four years, I wondered how in the world was I, going to continue with both of these passions? I thought maybe if I went to medical school and put together chemistry and psychology with research, because I was still very research oriented, that would be the way. So I applied and was accepted at the University of Buffalo, School of Medicine. My idea of going into research where I could combine chemistry and psychology really worked out. I went through medical school with the idea of going into psychiatry and in the year book it said I was the only student to keep the same specialty through four years of medical school. After graduation I did a rotating internship at E.J. Meyer Memorial Hospital, which was the county hospital. I have always been oriented toward public service with a strong research interest. While I was starting residency a huge change...
in psychiatry came about. Medications to treat mental illness came to the field, where before psychoanalysis had been the prevalent orientation.

WC: What year are we in, in the mid-1950s?
JL: It would be July 1958 that I started my internship. I went on to do two years of psychiatric residency in Buffalo at Meyer Memorial Hospital, which was like a small Bellevue. It was the place where the courts and police brought people if someone was acutely mentally ill, before going on to another facility.

WC: What were the drugs available to you when you were a resident?
JL: The antipsychotic drugs came on the scene in the fifties. So, I came into the field at that time.

WC: Did they call them antipsychotics then?
JL: No, major tranquilizers was the terminology then. One of the first things I did, coming from a chemical background, was to make a list of the psychotropic drugs and try to group them in some way. It turned out to be valuable to people and my teachers picked it up and used it as a teaching guide for the other residents and medical students. The classification I used, and that appealed to me, was psycholeptic, psychodysleptic and psychoanaleptic, meaning drugs that slow you down, make you go sideways or speed you up. As far as therapeutic classes were concerned, for the psycholeptics it was major tranquilizers, which we now call antipsychotics, and the minor tranquilizers, which we now call anti-anxiety drugs. The big ones at the time, we don’t even think about them much now, were meprobamate (Miltown), chlordiazepoxide (Librium), and diazepam (Valium) came on the scene. As psychoanaleptics, the antidepressants were the other big therapeutic class; the tricyclic antidepressants, prominently imipramine (Tofranil). Of course, there were no SSRI’s. The monoamine oxidase inhibitors came onto the scene a little bit later with iproniazid (Marsilid) being the first one. The residency program at the University of Buffalo, a private school then, had no research orientation whatsoever. In undergraduate school, I became interested in research through Saul Mouchly. I had a couple of summer Fellowships to do research, but there was no psychiatry research there, so, I worked in the surgical lab, where Saul was interested in hepatic coma and ammonia because it was thought to be the offending agent. I helped develop a method for measuring blood ammonia and that was to become my honors thesis; it was the first piece of research that I ever formally wrote up. In the residency, my interest in research continued and I was perplexed because when we used the antipsychotics or major tranquilizers I would give them to people and some people responded beautifully and some didn’t respond at all. I couldn’t understand why we had responders and
non-responders since clinically they looked so similar before treatment and we gave them the same dosages of the drug. Given my background in chemistry, I thought it must be a difference in metabolism. At that time, we didn’t have all the elegant methods that we have now and the way you measured phenothiazine metabolism was to collect urine and do something called the Forrest test, which was a color test. The developer, Irene Forrest, was a biochemist in Palo Alto. I put together a makeshift lab and found there was a problem with the Forrest test because some normal compounds like indican, interfered so you could get high or low readings, depending upon the interfering substances. That was the basis for the first publication I had in 1961 in *The American Journal of Psychiatry*.

WC: So, that was your first publication?
JL: That was my first publication.

WC: At that time the Korean War was on. Did you have any involvement?
JL: In my second year of residency I got a notice from the draft board and I knew about this program called the Commissioned Officer Residency Deferment program, CORD, of the Public Health Service, which said if you agreed to go in after residency you could be deferred. So, I joined the CORD program and didn’t go to Korea. When I finally did go into the Public Health Service I was assigned to the Hospital in Lexington, Kentucky, and that led into another era of my life. While I was still in Buffalo, I wanted to pursue a PhD in pharmacology so I talked with Doug Riggs, the chairman of pharmacology and he was interested that I was moving toward it but my chair, Saul Small, did not want me to do it and he prevented me from going into a joint PhD program. When I found that out, it soured me on him and Buffalo because he was somehow threatened by the fact that I wanted to get a PhD and an MD. Saul was a terrific teacher, but he taught me a lesson about not thwarting the aspiration of young people but helping them to go in whatever direction they wanted. That is something that has stayed with me through my career. A lot of my colleagues from Buffalo stayed there, but I moved on.

Because of my interest in the metabolism of phenothiazines, I found a biochemist, Herb Posner, at Saint Elizabeths’ Hospital in Washington, DC, where there was the Clinical Neuropharmacology Research Center, the CNRC, part of the NIMH, headed by Joel Elkes. I couldn’t get into that because it was a government program so I applied for residency at Saint Elizabeths Hospital. I went there as a third year resident, but was assigned to the William A. White building where the CNRC was located.

WC: Who were the people doing the research at CNRC at the time?
JL: Joel Elkes headed it up and Fritz Freyhan was the clinician psychopharmacologist who was there with a whole array of other people. Mimo
Costa and Steve Szara were there with a large interdisciplinary group. My job was to run a ward of female patients, who were chronically mentally ill and who had been at Saint Elizabeths for a considerable period. In the basement of the same building were the laboratories, so I did the phenothiazine metabolism research with Herb Posner, while running the ward.

WC: When did the CNRC start and how long did it last?
JL: It had been in existence about four or five years. Over the years it morphed into becoming a much more central part of the NIMH intramural research program.

WC: That did have a long strong history, didn’t it?
JL: It did and it was very interesting. Joel Elkes was a pioneer in our field and honored by this group and many others. His goal was to bring basic scientists and clinicians together so that they could learn from each other. Now we give it another name, translational research, but that is what he was after. He created a common room where we could have coffee or tea everyday around four o’clock and the idea was to bring the basic scientists and clinicians together. But what I observed was that the basic scientists and clinicians each went into their own corners and, unfortunately, cross communication didn’t occur. In order to get basic and clinical research and translational research going it is more efficient for it to be in one individual’s head. The idea of people developing a common approach to a problem will only happen if they jointly have the idea and the desire, so it has to come from the bottom up, not from the top down. That is something I think is still true. The MD, PhD and programs like that have been vital to moving the translational area ahead.

WC: What happened next in your career?
JL: I was at Saint Elizabeths for only one year to complete my third year of residency. While I was there, a man by the name of George Cosmides, who was a PhD pharmacologist, came to visit Herb Posner and was working at something called the Psychopharmacology Service Center at the NIMH. This was set up in 1956. A few people went to Congress and said these new drugs are going to revolutionize psychiatry and nobody is studying them so the NIMH ought to have programs that would. The NIMH, at that point, was not interested in psychopharmacology but congress appropriated two million dollars and created something called the Psychopharmacology Service Center (PSC); its first chief was Jonathan Cole. Jonathan is still around and is here at this meeting.

I owed my two years to the federal government for being deferred from the draft and when George Cosmides came around in the CNRC and saw my interest, he said I would love working at the Psychopharmacology Service Center, so he would see if he could get me there. I had been
Jerome Levine

assigned to the Division of Hospitals of the Public Health Service, so Jon Cole tried to get me released to go to NIH. That wasn’t possible so I was assigned to the U.S. Public Health Service Narcotics Hospital in Lexington, Kentucky and moved there in 1962. In some ways that was a lucky break. I met another fellow who had been assigned there that year, Arnold M. Ludwig MD, who had a research orientation. After the first few months we realized that we were green around the gills and the addicts knew much more than we did about addiction. We also realized that we didn’t have the foggiest idea of how to treat them. So, we did our administrative duties, retreated from patients and advanced into research. Arnold was interested in hypnosis and was trying to use it to control the withdrawal process. I was interested in discharge rates, why some people got out and why some other people didn’t. Another two-year-person, who wasn’t a psychiatrist, was working in some area at the Addiction Research Center, I did not know about came one day and said, “Jerry, you ought to come over and see some of these addicts. We do pharmacologic tests with LSD and some of them have an experience that changes them completely and I don’t understand it. It doesn’t happen all the time, but you ought to see some of these people”. I went over, talked with them and was intrigued by what they said. Then I went to the literature and saw that hallucinogens of various sorts were able to bring about a sort of conversion experience in some people. It sounded like it was a religious conversion experience and I got intrigued by that. Arnold and I got to talking and wondered if there was a way we could make this potentially therapeutic experience to happen on a regular basis. We hit upon the idea of controlling the LSD experience through hypnosis, and named it hypnodelic therapy. We asked the patient to take LSD and during the half hour or so before it took effect we hypnotized the person to have more control over the LSD experience, rather than letting the drug experience go in whatever direction it took. Combining hypnosis and LSD sounds pretty far out but we were about as non-far out as one could get. Getting into this area we had a lot of contact with Abe Winkler, Harris Isbell, and others and came to appreciate the wonderful facility the Addiction Research Center was. We did several studies down there and when our two years were coming to an end, Jonathan Cole got back in touch with me again because LSD was being touted as a very important treatment for alcoholism, psychoneurosis and other things. He wanted someone to set up a program to test whether there was any validity to the claim that LSD could be used as a therapeutic agent. He recruited me to do that in 1964 and I wound up going to the NIMH; two years earlier I had hoped to go there, but now I came with expertise and a mission.
WC: When you moved there, where was it located?
JL: Above the State National Bank in Bethesda, not on the NIH campus. The PSC was an extramural part of the NIMH. In other words, they didn’t have laboratories and patients but worked by giving grants, contracts and designing studies. We only had offices and we didn’t do the research directly ourselves.

WC: About how long were you with that Center and tell us the kind of the things that happened during your tenure?
JL: I stayed with the NIMH a little more than twenty years and set up, using grants and contracts, a number of studies of LSD as a treatment agent. One of the studies that I was most directly involved in, was with Arnold Ludwig, who had moved to Mendota State Hospital in Madison, Wisconsin, as the director of research. He and I designed and set up a study to test whether the hypnodelic therapy worked for people with alcoholism. We designed a controlled clinical trial with a follow up, because we could never do follow ups with addicts at Lexington. We could only do psychological tests and look for changes. We did that study and NIMH funded a number of other studies at the same time. The study we did was recognized by the American Psychiatric Association and Arnold and I won the Hofheimer Research Prize.

WC: That was the leading prize the American Psychiatry Association gave at the time?
JL: It was. That was in 1971. When we finished that piece of work we wrote a book together, *LSD and Alcoholism*. Arnold Ludwig is lead author, I am the second and there was a third author, Mr. Stark, a research assistant, who was very helpful in the study. Writing that book ended an era for us. We were excited by LSD as a potential treatment; but it had played out and we had our answer; hypnodelic therapy didn’t work. Most of the studies that were supported by the NIMH were negative; LSD wasn’t useful as a therapeutic agent.

WC: Let me ask you a broader, less personal question. When did control studies come to be the main way to evaluate efficacy and what role did the Center play in developing that as the standard?
JL: That’s clearly what changed our field and all of medicine. It was when the Kefauver-Harris amendments were passed in 1962 which required that drug manufacturers’ show proof of efficacy of medications, not only if they were safe, before they could be marketed. In the mid-1950s and early ‘60s, a rash of antipsychotics, antianxiety and antidepressant agents came to market. The companies advertised they were effective but there weren’t controlled clinical trials to back them up. With the psychoanalytical orientation of the field there was also a lot of resistance to...
using these drugs. The PSC came into being partly to test whether these drugs worked and to give guidance to people on how to use them. Jon Cole, one of the most important people in developing this field, designed a number of controlled multicenter studies, which met rigorous criteria for proof of efficacy of medications. That was one direction the PSC went in. He also created a number of units around the country and world that were called Early Clinical Drug Evaluation Units, ECDEU. They were usually located in academic settings and people were given support to do clinical trials of new medications without being beholden to the drug company. When I came to the NIMH, I liked the extramural way of working, of seeing what the problems and needs were and being able to give grants and contracts to investigators who wanted to work in the field. Jonathan saw that I understood this way of working and asked me to become his deputy. We had wonderful people working with us.

WC: When did you become deputy and then who were the other people?
JL: I came to the NIMH in 1964 and became deputy about two years later. The terrific people Jonathan had recruited were both my teachers and colleagues and I got a jump start working with them. Jon Cole left NIMH in 1967 and I became Chief about a year later. We covered both pre-clinical and clinical psychopharmacology. On the pre-clinical side, there was Daniel Efron, who was very influential in the ACNP. Dan was able to pick out research talents like no one I ever knew. At that time we used to run our own study sections, and review committees. There was no separation between these study sections and the funding program. They were both together under the PSC and later under the Psychopharmacology Research Branch. Dan set up some of the best study sections I have ever seen. It was nice to have on these study sections people like Julie Axelrod, David Hamburg and Paul Greengard; two of whom have received Nobel Prizes. Sitting in on study sections you heard from the best people in the world asking for funding. To have people like the ones I mentioned reviewing grant applications was a joy and the best possible post doctoral tutorial experience. The other thing we did was site visits. On almost all of our grant applications we visited the places, so not only did you see the ideas written down, but you interacted with the investigators. We used to have two people from the study section and one or two people from the Center go out; that was an educational process and creative process for the field, the investigators and NIMH staff. That was an important aspect of the funding process that is missing today.

WC: It was an important transition, when there became a separation between the programmatic and review side. How did that take place?
JL: One of the people Jonathan Cole recruited to the PSC was Gerald Klerman, another giant in the field. He helped Jonathan set up controlled clinical trials and the ECDEU program in the late 1950s or early ’60s. Gerry went on to a very significant career at Harvard and Yale. He then came back to the federal government as head of ADAMHA, a conglomeration of the NIMH and the Drug Abuse and Alcohol Institutes. At that time there were complaints that program people were influencing review committees too much about which grants got approved and funded. There might have been some of that, I don’t know, but the intervention was to split review from program and not have program involved in funding. That coincided with a time when money was starting to become short and so staffing of the review program never got to where it should have. It was a bit like what happened with the community mental health centers when the money ran out for them. Consequently, it weakened the review system and you didn’t have people running the study sections who were really knowledgeable interacting with the review committees and the field. As a result the NIMH became a less interesting place for people to work. Before, you could see applications come in, see them funded and follow them as a project officer over time. Your role was a lot more interesting than just doing review or program.

WC: Who were some of the other people working with you at that time?

JL: Just as Dan Efron and Earl Usdin were very productive persons on the preclinical side, Sol Goldberg and Nina Schooler contributed mightily to the clinical side in schizophrenia. Ron Lipman and Al Raskin worked on clinical studies of anti-anxiety drugs and antidepressants respectively. We recruited Bob Prien from the VA, who was instrumental in getting lithium studies done; lithium wound up on the market because of them. Another guy was Mitch Balter who was interested in pharmacoepidemiology; finding out how much medication was used and if it was being used well. Mitch retired from NIMH and died at a young age.

WC: Was Gerard Hogarty another person that worked in the center?

JL: Primarily he was supported by the center. Gerry Hogarty was certainly influential and was one of the people involved in the multi-center clinical trials, actually in one that was run out of Springfield State Hospital, not far from Maryland Psychiatric Research Center (MPRC). He liked that way of working and when he saw what you can do with clinical trials he was attracted to working extramurally. So he worked closely with Nina Schooler and Sol Goldberg in studies of schizophrenia and subsequently went to MPRC, where he contributed to your research program and then on to the University of Pittsburgh.
WC: You have talked about evaluating efficacy. You also have had a long history of being concerned about adverse affects. How has that played out?

JL: As context I would like to describe some NIMH organizational history of the clinical evaluation process before I get to safety and adverse effects. The PSC, which then became known as the Psychopharmacology Research Branch (PRB), and, then the Pharmacologic and Somatic Treatments Research Branch (PSTRB), had changed its name, but not its mission over the years it existed. Earlier, I mentioned that, as part of its program, about twenty Centers were set up to evaluate the ability of new drugs to treat psychiatric disorders. These Centers were not primarily involved in multicenter trials following a common protocol. They each chose what drugs to study and what protocol to follow. Jonathan Cole and Gerry Klerman had the idea that they should come together and meet once or twice a year to exchange the results of their studies. We found that it was very hard to know whether Don Gallant in New Orleans, who was using the Purdue Pegboard, and let’s say, Hy Denber in New York who was using some other outcome measure, were agreeing or disagreeing about findings with each other. So we set out to see if we could set up a standardized evaluation system where there would be a cafeteria of measures that had been vetted and were reliable and valid measures of psychopathology and psychiatric functioning. Everybody could design their own study but if they used standardized scales we would know whether they agreed or disagreed with each other on the efficacy and the safety measures. From that idea, we developed something called the Biometric Laboratory Information Processing System (BLIPS), and the ECDEU assessment manual, which listed all the scales. It was a way you could record data. Those OpScan forms were then sent to the biometric laboratory at George Washington University, which the NIMH supported, to have data analyzed. The analysis was returned to the investigator to write up and publish the results. This approach became the standard in the field. In fact, we used to see the output put directly onto slides.

Around this time the FDA started to want guidelines for clinical trials in different therapeutic areas and the existence of this ECDEU way of studying medications using standard forms became the basis for a large part of what they required. The danger of that is that you rigidify the field so that everybody does studies exactly the same way. I must say I think that did happen to a certain extent. Recently we are moving away from that. There seems to be more interest in developing new methodology. Donald Klein’s suggestion of starting all study participants on medication, selecting those that respond and taking half of those off medication but following them, will pharmacologically dissect the group into true
responders or nonresponders. This may be a new way of gaining more information.

In the BLIPS, used by the ECDEU investigators originally, scales like the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impressions (CGI), were put into the ECDEU assessment manual, which is still distributed by the NIMH. It was done in 1976 and is still requested for trials. Now, on the safety side, this is an area I had an interest in, because I could see we were not doing an assessment of side effects nearly as well or in an organized way as we were with efficacy. I tried, unsuccessfully, to recruit a number of people to have careers in side effect assessment. But side effects are not as interesting as efficacy to people. Nina Schooler and I had been instrumental in developing the Abnormal Involuntary Movement Scale (AIMS) as part of one collaborative clinical trial, looking at fluphenazine. So we got to work on developing an instrument for side effect assessment. We thoroughly thought through the problem and came up with something called, Systematic Assessment for Treatment Emergent Events (SAFTEE). It is not widely used because it takes a long time to complete but is the best thought through system for evaluating side effects. We knew it was a Model T, it wasn’t beautiful, it wasn’t sleek and it wasn’t fast, but we hoped the field would pick up on it and use the principles behind it to develop a Corvette. That is not happening rapidly, but with a renewed emphasis on side effects I think that we will have to return to how we collect data in a more systematic way.

WC: How did your work connect with the ACNP, and the kind of organizations forming around the world with an interest in neuropsychopharmacology?

JL: Morris Lipton used to say that the PSC was the yellow pages of psychopharmacology. In other words, if you wanted to know something about what was going on in the field you could just call up the PSC and somebody would put you in touch or know what was happening. That happened because we were involved with organizations that got created like the Collegium International Neuropsychopharmacologicum (CINP) and the American College of Neuropsychopharmacology (ACNP). All of us were used to working in an extramural way, participating in these organizations. One of the things that I did when we were developing guidelines and ways of doing clinical evaluations was to sit on the ACNP’s, Government Industry Liaison committee. I asked Burt Schiele, the chair of that committee to help put together a set of guidelines of how to evaluate psychiatric drugs. He liked that idea and, jointly, the NIMH and the ACNP produced a book contributed to by many members. We called it, Principles and Problems in Establishing the Efficacy of Psychotropic
Agents, but a lot of people referred to it as the Blue Book. That began the process of guidelines for trials and the ACNP and NIMH worked very closely together. Then, there was the whole series of Decade of Progress reports. In the First Decade of Progress book Dan Efron was extremely involved and saw that the government published it, although the ACNP held the meetings, requested the manuscripts, and put the book together. Jonathan Cole became president of the ACNP and there was a very close working relationship between ACNP and staff in the PSC, who had their own expertise and qualified to be members because of their own accomplishments.

WC: You stayed about twenty years, why did you leave and what happened next in your career?

JL: I got to be fifty years old in 1984, had been at the NIMH for about twenty plus years, and felt I could stay because I liked what was going on. But I also thought I ought to look around and see what else was going on and decide whether I wanted to end my career at the NIMH or try something else. One of the places I thought of was the MPRC where you had changed the place from doing LSD research to where cutting edge schizophrenia research was going on. I had become interested in schizophrenia research because of the work with antipsychotic medications and clinical trials. You and I got together and talked about whether there was a role for me at the MPRC, if I was to leave the federal government. Working with you and MPRC, not having to move my residence, the fact it was on the grounds of Spring Grove State Hospital, and tied to the university appealed to me. I hoped I could bring to MPRC some of the ideas and ways of doing evaluations and developing new instruments, perhaps helping younger people with research careers. In fact we did get an NIMH grant for training psychiatrists to become research psychiatrists.

WC: You headed up the first T32 support that we had for the Fellowship program.

JL: A number of people came out of that program and it spilled over to the university program. So somebody like Ahmed Elkashef, a resident at Maryland, while he didn’t take a formal Fellowship, benefited from the research training we put into the residency program. He went on to have a long federal government research role. Lisa Dixon went on to a research and academic career in the services research and schizophrenia area, teaming up with Tony Lehman. It was a transition, learning how to work directly with investigators, rather than the kind of relationships I had at the NIMH. You made that transition a great experience for me and I hope I contributed a little to the growth and stability of the MPRC program.

WC: You did.
JL: I had been at MPRC about nine or ten years when I got a call from Gene Laska at the Nathan S. Kline Institute for Psychiatric Research (NKI). I had also known about the NKI because when I was at the NIMH we had given some grants to them. I had worked with Gene, writing chapters on methodology and he had been a presenter at several conferences I had organized. Gene told me he had a deputy director position open and asked if I was interested in looking at it. It is a very exciting time, they were about to have a new building, an imaging center and two twelve bed clinical research wards.

WC: What year?

JL: That was 1994. It’s unusual at the age of sixty that one has an opportunity to get into a growing research program with a new infrastructure and to help to create, and reinvigorate it. I thought this is something I could do. NKI was affiliated with NYU School of Medicine and I was also appointed Professor of Psychiatry there.

WC: That’s been a terrific position and the institution has done awfully well. It has been nice to see how it’s developed. So what is next for our field and what is next for you?

JL: I think the field is at a very exciting time now. I am still as enthusiastic and have as much fire in my belly as I ever did. Having lived through the era of neurotransmitters, when we thought we had the answer, then seeing imaging come on, seeing those fantastic pictures Herb Pardes was so effective in presenting to get Congress behind mental health and double the budgets and so forth; seeing all those developments is exciting. A lot has happened but, clinically, not much has changed. We have new tools; we have genetic and imaging techniques and we have learned a tremendous amount but we haven’t been able to hit the home run. We haven’t been able to turn these techniques into different kinds of knowledge that let us treat patients better. When you see a patient and decide the best medication treatment its still by trial and error. It’s very much the same as when I was in residency. Maybe we are going to learn personalized medicine from genetics. But, having been excited by so many breakthroughs I am a bit cautious about how soon we will have a dramatic breakthrough that will change our field.

WC: Anything else you want to add?

JL: Just how grateful I am. I happened to come along when our field was emerging and it coincided with my interest and it is so exciting to be able to participate. There are a lot of definitions of utopia and mine is when someone will pay you for the work you love to do; that’s how I feel about psychopharmacology. I have had a rewarding career and, hopefully, I have given something to it. It’s been a wonderful, wonderful ride.
WC: It sure has. You have contributed so much. You were there as things were beginning and have seen a lot of change and development in the field. You speak to the frustration of how we can make a new impact on mental illnesses but you are still active in your career. What is your plan for the immediate future?

JL: I probably will retire sometime in the next five years. I can tell my medical school education is wearing out and can’t keep up with all these molecular and genetic basic neuroscience advances. In the field of clinical trials, I still feel that I am very current and understand the methodology and the instruments. But the basic side has advanced so far that my training has not kept up. I am going to my 50th medical school anniversary since graduation in 2008 in Buffalo. That education served me well, but it’s getting worn. I am delighted about how many young people have come into the field and the growth of the ACNP. There certainly are people who have taken over and will make the field prosper.

WC: Thank you a lot for telling us your piece of history.

JL: I knew it would go easily and it certainly did. Thank you.
CT: My name is Carol Tamminga and I’m interviewing Dr. Herbert Meltzer for the Archives of the American College of Neuropsychopharmacology.

HM: Thank you, Carol.

CT: So we have the opportunity to talk about what you’ve done in our field and where our field is going in the future. Could you tell us where you were born and something about your early education and interests?

HM: I was born in Brooklyn and educated in the public school system of New York City, a fine education, before I got interested in science at Cornell in College. I started out as a philosophy pre-med major and fell in love with chemistry. After graduating from Cornell, I did a year of chemistry at Harvard. But the call to be a doctor was very strong and I went to Yale Medical School where I worked with Peter Green, Nick Jarman and Dan Freedman. My interest in neuropsychopharmacology was divided between basic and clinical research but the key influence on my career development was Tom Detre. He was my first coach as a medical student with his phenomenal skills as a clinician. It sounds strange but true; the career I have had, integrating basic and clinical research, is the epiphany of moments I had early on in those psychiatric wards. I’ve since turned down lots of industry and academic jobs because I like to do what I do.

CT: Tell us about the influence that Tom Detre had on you?

HM: I’ve written about this in a book, so I’ll just summarize it. I was assigned a woman with a psychotic depression and worked her up very carefully. Tom said to me, what you’re doing is all wrong; let me show you what to do. So he brought the woman into an amphitheater to present to the medical students. Tom is very confrontational and he told her, “This was your responsibility; your husband didn’t do this to you”. And that was transforming for her and for me. As they took her out of the amphitheater she turned around and said to me, “No one will ever humiliate me like that again”. I could see that the art and skill of being a psychiatrist was something special and wanted to emulate Tom. On the lab side, Dan Freedman and the terrific pharmacology at Yale set me on my career path.

CT: This happened when you were a medical student?

HM: Yes and it would have been in 1961. Then, I did an internship at Mass Mental Health before I went to NIMH; that was another transforming experience. Ironically you go there expecting research skill enhancement, which I got, but more importantly my whole approach to treating schizophrenia was influenced by a man named Jack Durell. It was at
that time I realized, what is now pretty standard, that bipolar disorders and schizophrenia are a part of a continuum. I discovered by a series of muscle fiber biopsy findings that were common to bipolar disorder and schizophrenia. I became involved with CPK and postulated in my review in the Schizophrenia Bulletin that there had to be genes common to these diseases that affect the development of the synapses and neuromuscular junction. Hans Moises from Berlin wrote that, based on my paper, he saw those genes as candidate genes and was looking for them. So, at one time, I was the world’s expert on CPK activity. I’d also discovered the CPK increase in neuroleptic malignant syndrome.

CT: What did you do after your post doc at NIMH?
HM: I made a terrific decision to go to Chicago and join Dan Freedman’s department. The main attraction was the research unit at Illinois State Psychiatric Institute. I continued the CPK work in muscle for a number of years and then, in conjunction with Ed Sacker, I got into neuroendocrinology that I’ve turned into a neuropharmacology driven discipline. I did studies on serotonergic and dopaminergic regulation of prolactin and growth hormone and worked with cortisol and ACTH. In 1985 I moved from Chicago to Case Western University in Cleveland where I did a series of neuroendocrine challenges with MK212, structurally 6-chloro-3-(1-piperazinyl) pyrazine, a $5\HT_{2C}$ antagonist, and m-chlorophenylpiperazine (mCPP) morphine. I’m still working with those data in mice to characterize mCPP and MK212. I’m getting ahead of the story, but I’m trying to show that there was continuity rather than disjunction in my work. Then, not so many years ago, I showed that atypical antipsychotics can markedly increase CPK in some genetically vulnerable subjects.

CT: Can you talk more about your time at NIMH, who was there and how your research ideas evolved?
HM: We were all part of Seymour Kety’s group; Dennis Murphy was a clinical associate, Fred Goodwin, Will Carpenter, and John Strauss were all there, but I was Durell’s only associate. In the middle of my first year he and the NIMH parted company so I was given the responsibility to run the ward on my own until Fred Snyder, the sleep researcher came, followed by Dick Wyatt and David Kupfer. Together we did some sleep studies in schizophrenia. Then, I started my own work with CPK. I was only the second person in the world to get onto that.

CT: How did you get into CPK?
HM: Hans Hippius, professor at Munich, wrote the first paper on CPK. He thought it was coming from the brain. I confirmed his findings about elevation in CPK in schizophrenia and extended it to bipolar disorder. I found the same thing in mania, psychotic depression and schizophrenia,
so I’ve been one of the people from the early days; we’re talking about 1968, saying that there was a common pathophysiology to the major psychiatric disorders.

CT: What gave you that idea?
HM: At Mass Mental Health, Gerry Klerman taught about Griesinger and the concept of unitary psychosis. He also taught that Kraepelin ended that era. So, I looked at my findings in an historical context and wasn’t totally surprised to find common features in schizophrenia and bipolar disorder. I organized a conference for the Association of Research in Nervous and Mental Disease in the mid 1970’s and edited the proceedings. The title was, *Exploring the Similarities and Differences Between Bipolar Disorder and Schizophrenia*.

CT: Was bipolar at that time separated into bipolar I and II?
HM: I don’t know if the classification system did, but I certainly did.

CT: I love to listen to the history of how your ideas evolved. Could you say that you had a central theme in your research from the beginning? How would you characterize that?
HM: The link would be the work I’ve done in drug discovery, drug development, understanding and treating the major psychoses. I had a Center Grant from NIMH for fifteen years and the title was Comparing Bipolar Disorder and Schizophrenia. It was a transforming experience to be the Center Director, because in addition to my own work, it provided the resources to bring together a group of superb people to pursue a few things in depth.

CT: When did the Center start?
HM: In 1978, and it lasted until I moved to Vanderbilt in 1996, so we’re talking about almost eighteen years.

CT: Where were you when it started?
HM: At the University of Chicago. I stayed for eleven years in Chicago and then moved to Case Western in Cleveland.

CT: So, after you finished your post-doc at NIMH you moved to Chicago?

CT: Can you tell us about the research environments and the differences and strengths you found in each of those three places?
HM: In Chicago; although it was a very strong institution, I was isolated. I don’t think there was anyone doing human research of the kind I was doing, certainly not in schizophrenia or bipolar disorder, but it was a very stimulating environment. My work involves both patients and the lab and you need an institution with the infrastructure for that and Chicago didn’t have it. Dan never built a clinical base, so I developed my own at the Illinois State Psychiatric Institute. When the leadership changed and was not interested
in research they closed the whole program. That was the signal to find somewhere else. Case Western was extraordinary in terms of how the head of the hospital and the board of trustees were deeply committed to what I was doing and made inpatient and outpatient resources available. And, because of the Center, I had a team of terrific people. Foremost among them was Bryan Roth, who wanted to work with me because of my interest in serotonin receptors and brain imaging. We did some of the first PET and MRI studies. Then, I came to Vanderbilt. Vanderbilt is an extraordinary place, never more so than now. It’s got phenomenal infrastructure for basic and clinical research. I say that, thinking about the support for imaging and for genetics. I’ve been working with the largest mental health system in Tennessee; I have four research clinics to provide patients for our studies.

CT: Now we have the chronology of your career could you tell us the central theme of your research?

HM: I consider myself, basically, a psychopharmacologist and secondly, a biological psychiatrist looking for the common cause of bipolar disorder and schizophrenia. I’m focusing on psychopharmacology because I use what I learn from drug treatment. My observation that clozapine was superior to other antipsychotics and, in addition, blocked tardive dyskinesia, in the mid-1980’s led Sandoz to develop the drug. We worked out the design for the US and for an international study. When the interim analysis of that data came back, I called the people in my lab together and said; we’re changing direction, we’re going to focus on clozapine, dopamine, and serotonin. That work eventually led to the development of the most commonly used drugs today for schizophrenia and bipolar disorder.

CT: What did you change from?

HM: We had been studying a variety of new treatments for schizophrenia and bipolar disorder, trying to come up with a serotonin and dopamine hypothesis. When I was at the University of Chicago I was among the first to give fluoxetine as an experimental treatment for depression. The very first patient I gave it to developed severe dystonia. We thought perhaps we got the drugs confused and gave haloperidol to the patient instead but it turned out we had given fluoxetine. That led me to go in depth into the role of serotonin in regulating dopamine. I wrote a long review article for Synapse and Floyd Bloom published it. Everybody else was still focused on dopamine, dopamine, and dopamine.

CT: So you used clinical pharmacology in patients to guide your laboratory research?

HM: Absolutely, but I’ve also done it the other way around. Everybody is interested right now in cognition and schizophrenia, and I was able to use animal models to get at that. The result was buspirone, a 5HT$_{1A}$ partial
agonist that might be a cognitive enhancing drug. We’ve done four studies and they’re consistent with that view, which came out of animal work showing these drugs enhance cortical dopamine.

CT: Who else was doing similar work or using similar strategies and what impact did that have on you?

HM: The muscle work with CPK has been picked up by several groups, particularly by the group at Karolinska that replicated all our major findings. The strategy we used in the neuroendocrinology work was also used by the late Ray Fuller at Lilly and Renee Kahn. I was the first one to use drugs like mCPP and MK212 in patients as a probe to try to get at a so-called window into brain pharmacology. Dennis Murphy was extremely important in that area of research outside of my group. There are a lot of terrific people now, who are trying to push the envelope on cognition. I was the first person to report that clozapine could improve cognition and it was very controversial at the time. All the major findings that I’ve made in clinical research have been replicated. But, obviously, not every study shows the same thing.

CT: You also showed, as I recall, not only that clozapine improved cognition but it had a real impact on psychosocial function. Can you talk about that, because it’s so important in people we treat?

HM: A key person in my career is a psychiatric nurse, named Sarah Burnet. She was head of nursing at the Illinois State Psychiatric Institute when I started in 1968. Sarah still works with me. She moved with me to all these places.

CT: My goodness!

HM: She’s one of those people with intuitive skills toward the seriously mentally ill, and Sarah has worked for thirty eight years with chronic schizophrenic patients. The psychosocial improvement in that group, both in an absolute and relative sense, was much greater for anybody who had the opportunity to work with Sarah. I was primed to look beyond improving memory to learn about its effect on psychosocial functions. I got interested in the psychosocial issues while working with Jack Durell at NIMH, contrasted with the Mass Mental Health center where they were narrowly psychoanalytical.

CT: What kind of effect did the psychoanalytical approach have on your career and have you used it or not?

HM: At the Mass Mental Health Center I had intensive training in psychoanalytically oriented psychotherapy but I never saw it as very useful as a primary treatment. People like Dan Freedman and Fritz Redlich were analysts, who saw the need to become more biological if the field was to move forward.
CT: And, they were your two mentors when you were a resident at Yale?
HM: Redlich indirectly but Freedman was my major mentor. The psychosocial treatment I’ve been interested in is much more guided by the milieu concept than individual psychotherapy.

CT: Are you still involved in inpatient treatment?
HM: Very rarely; although, my Chairman has asked me to set up a mental health clinic that would be part of the small psychiatric hospital Vanderbilt has.

CT: Have you ever had a private practice?
HM: I’ve never had a formal income generating private practice. I’ve been blessed with enough research and administrative responsibility that I’ve not had to look to that as a source of income but I have seen, in all the cities where I’ve been, people I personally follow, prescribe medication for, and see as needed.

CT: You’ve mentioned drugs you’ve had a hand in developing. Can you just tell us about the drugs that have been important?
HM: I studied phencyclidine, PCP. I was searching for an animal model of the muscle abnormalities and found the best one was PCP in stress. I did studies with it in humans, along with ketamine.

CT: I recall you did the first ketamine study.
HM: Working with an anesthesiologist, we used ketamine just the way an anesthesiologist would. We studied people before and after being given enough ketamine to sleep for an hour and we didn’t find anything. PCP was another story. I became impressed with how it can disorganize cognition and I was the first to report that it increased the turnover of dopamine. Perhaps the most interesting story is the work I did with melperone. It came out of my animal models. Melperone probably would have been the first world-wide atypical antipsychotic, except ironically, the Swedish people, who used that drug as an anxiolytic, dismissed it as an antipsychotic because it did not produce extrapyramidal symptoms.

CT: They had shown it was an antipsychotic?
HM: Somebody from the Karolinska Institute published four or five papers from at least two different studies. We went on to show that, just like clozapine, it is good for treatment resistant patients with minimal EPS. There is a company in the US that’s finally developing it but their focus is L-DOPA-induced psychosis.

CT: Then, did you leap right into clozapine?
HM: Melperone was after clozapine. I used melperone as one of the validating concepts for the serotonin and dopamine hypothesis. After clozapine came a slew of serotonin and dopamine antagonists. Now I’m in exciting work with a pure 5-HT\textsubscript{2A} antagonist, pimavanserin, showing it’s effective...
Herbert Y. Meltzer

in L-DOPA psychosis and can greatly potentiate risperidone. In a paper I just presented last night I showed we could take a sub-therapeutic dose of risperidone, add pimavanserin to it, and it worked faster, if not better, than a full dose of risperidone. And I think it is going to work in the same way with all the atypical antipsychotic drugs. For olanzapine you could cut the dose to about 3 to 4 mgs a day.

CT: And cut the side effects?
HM: Yes, dramatically cut the side effects and maybe enhance efficacy. The serotonin effect can be, by itself, antipsychotic. I’m thinking in terms of therapy in the maintenance phase. Between endogenous cycles of psychosis, you probably don’t need that much dopamine antagonism. Using pimavanserin one should be able to titrate, the dose of atypical neuroleptics. I’m in favor of having this particular kind of adjunctive therapy as, an add-on, as opposed to one pill with a fixed dose.

CT: Would you use these pure 5HT_{2A} antagonists with first generation drugs?
HM: We’ve tried that. They don’t work as well with a pure dopamine-D_{2} blocker, at least not with haloperidol.

CT: You’ve talked about a few people you’ve collaborated with and people who have been important as your supervisors or mentors who you’ve patterned yourself after. Can you talk about some of the people you’ve trained?
HM: I would be remiss if I didn’t begin it with you!

CT: Thank you very much.
HM: It was a delight to have you as a resident on that research ward. I have trained several leading Japanese psychiatrists, going back to the 1960s. I’ve had about 13 or 14 of them and 6 or 7 of them are now Chairs of Psychiatry in Japan. A new one is just coming next spring. Within the US, there have been a lot of key people. I think the one I had the most influence on, and we still collaborate a lot, is Bryan Roth, who heads up the new research program at the University of North Carolina. Steve Paul was briefly in my lab before he was in Fred Goodwin’s. Marty Lowy is another guy who’s gone on to a major position in industry.

CT: What is your involvement in training and teaching now at Vanderbilt?
HM: I teach residents one of these rotating courses. I teach psychopharmacology to the medical students and the residents and, administratively, I help chair this or that subcommittee on neuroscience.

CT: Can you talk about the ACNP, when you joined it, and what your experiences have been?
HM: It was the Shangri La we all wanted to go to when it was starting and Dan Freedman brought me here first, probably in the 1970’s. I’m not sure exactly when I became a member, but probably 1975 or so. I was
treasurer for a year, probably 1982 or 1983. Then I was the youngest President of the ACNP. I also chaired the Program Committee twice and was the person that introduced posters to the ACNP.

CT: That was important.
HM: I had seen poster presentations at the Neuroscience meetings and thought we ought to do it here. So the presidency was a tremendous opportunity.

CT: What year was that?
HM: It was 1985. I always look toward this meeting as a pivotal calendar event, an opportunity to learn the latest research, and see old friends.

CT: Both of those things.
HM: Yes.

CT: You’ve been involved in other major organizations also?
HM: The other major one was the CINP. I was president between 2004 and 2006, culminating in a huge meeting in Paris. They’re very different experiences, being president of the CINP and the ACNP. In the CINP you could be part of a broader international community of neuroscientists. You get some of that at the ACNP, but not enough. From the CINP I made contacts and established research relationships that would never have happened had I not had that international exposure.

CT: Could you say something about the honors and distinctions you received?
HM: The Efron and the Hoch Awards have been incredibly meaningful to me and also a prize from Vanderbilt. Vanderbilt has a Chancellor’s Award for Lifetime Achievements, called the Sutherland Prize, and it’s open to any faculty member. I was nominated by a member of our department and received it three years ago.

CT: Sutherland, of course, was the Nobel Prize winner at Vanderbilt, so it’s obviously a prestigious prize.
HM: I also received the American Psychiatric Association Lifetime Achievement, Biological Psychiatry Gold Medal, and the Lieber Prize. One of the things that I’m most proud of is that I was one of the original founders of NARSAD and their first Executive Director.

CT: And you’re still on the NARSAD board.
HM: I chaired the NARSAD board helping it grow to where it is now. In some sense that is even more important than any of the individual research studies I do.

CT: Could you talk more about your involvement with NARSAD, and how that’s so important?
HM: We started with John Strauss, Sam Keith, and I’m not sure if Will Carpenter was there but we had enough money to give two grants. I chair the group that looks at the young investigator applications and that’s been very
exciting and challenging. I do it pro bono, and it takes about two weeks to go through eight or nine hundred applications and make sure we review them properly.

CT: It’s amazing that NARSAD is the kind of organization that gets people to commit two weeks of their lives just to the mission.

HM: I know how important those young investigator awards are. I have a new brochure about NARSAD to begin fund raising.

CT: You’ve seen the field change so much over the years from when you first started out working with Seymour Kety at NIMH in psychopharmacology. Could you give us your perspective?

HM: I would say biochemistry, neurochemistry and post mortem attempts to identify a “lesion” in the brain were the predominant strategies in the early stages of my career. Psychopharmacology was also much more prominent than it is now. There wasn’t just industry then. What is striking is the shift into genetics and imaging, in particular. From about 400 NARSAD applications maybe two hundred and fifty are now in genetics or imaging.

CT: Goodness gracious! So, you get a bird’s eye view of what young people are doing?

HM: Yes. And, there is almost no application from people testing hypotheses about the biochemical abnormalities or the physiology side.

CT: Can you tell us about your family?

HM: I’m married forty seven years to Sharon Bittenson, who is a PhD in English Literature. When I moved from Chicago to Case Western she kept teaching in Chicago, so we had a commuting marriage and that’s one of the reasons why I’ve been able to publish as much and do as much, because when she’s away I work all the time. I have two kids, one in medical school, and another, David Owen Meltzer, who is Professor at the University of Chicago. I’m now known mostly as David Meltzer’s father, rather than Herb Meltzer, because he does world class work in health economics. We’ve had him speak at the ACNP. And, just last night, we presented his poster.

CT: In what area?

HM: His focus is general internal medicine. He recently married and has no children. But, my daughter is an extraordinary woman. She is a Harvard and Yale undergraduate and a very successful real estate lawyer in Chicago. She has two delightful kids.

CT: Both your children live in Chicago?

HM: Yes.

CT: You managed your family life with your professional activities by saying that you have more time to publish when you lived separately. Do you want to say any more about that? That’s a question young people ask all
the time; how does somebody like you, who’s so invested in many interesting things, spare time for a family?

HM: The time that we have together, because it’s limited, I do focus on doing things together. I have a very strong interest in music and photography and my wife shares some of those. So we spend time there. But there is something inside me, and I think in anybody who does this much, wanting to find answers to a lot of questions. I go after too many issues, in some ways.

CT: Let’s spend the last few minutes we have talking about your vision for the future.

HM: I’m very confident we’ll have major changes in diagnosis and treatment of mental illnesses. I actually felt we would be there by now. In terms of treating schizophrenia and bipolar disorder, I think that genetics may disclose some things but the important breakthroughs will come from preclinical people looking at animal models. I’d like the field and the ACNP to come back to its roots in psychopharmacology. We need to train many more people who are skilled in this and continue to enhance our methodology for assessing psychopathology and biomarkers. I see diagnostic tests for the serious mental illnesses coming from such efforts. Probably within a year or two we will be ready for use of a diagnostic test for schizophrenia.

CT: Can you give us a clue?

HM: I can tell you a part of it. I’m working with Professor Mark Brennon at the University of Kentucky and he’s found a particular gene, sulfur transferase on chromosome 22 that looks like it’ll be a key. But that is only part of what we’re doing. The general methodology that Mark has developed can lead to early identification of disorders, using genetics and other biomarkers and to treatments that intervene in psychosis before cognition is affected. One of the things I’ve found already is that cognitive impairment in bipolar disorder is almost as severe and widespread as in schizophrenia. Cognition will come again to be seen as a central problem in schizophrenia. It’s crucial, and out of that, new treatment directions will emerge.

CT: People have, of course, differences of opinions about genetics and how genetics will contribute to identifying the molecular pathology and affect drug development. I look at diseases, like Huntington’s disease, where we’ve known the gene for a long time, and seen the difficulty of translating that knowledge into treatment. What are your thoughts about that?

HM: We’re interested in breaking schizophrenia down into psychoses related to cognition and I think we can find the genes for those. They’re not going to be unique to schizophrenia. I’m working on 5HT2A receptor polymorphism.
Our focus is on the phenotype of the people we’re studying and what genes are producing that. I have some excellent stuff that I think will be coming out this year on multiple candidate genes. Some pharmaceutical companies have completely abandoned the genetic approach to find targets for treatment. But pharmacogenetics will someday predict who gets what side effects and who’s more likely to respond. I think that will be available within a half dozen years.

CT: What is the most important thing to say about you as a scientist?
HM: My passion for both basic and clinical research; integrating advances in one field into the other. As past President of ACNP and CINP, getting involved, heavily, in these organizations enriches one’s life and gives a great deal back to the field. I probably could have done a lot more research in the six years I helped run the CINP. That was tremendously demanding and it was only after I’d finished, I realized how much it took away from my research.

CT: Hard work has been a big part of your career.
HM: It’s never felt like work. It’s been things I wanted to do. Right now, I don’t have to work. I have excellent retirement funding from my three universities, but to stop work would be to stop the most meaningful thing I’m doing. So, I don’t feel its drudgery.

CT: It captures your interest, for sure.
HM: I should mention I have two very strong interests, one of which I finally decided to do. I’ve gone back to the piano and I’m playing jazz now.

CT: Do you take lessons?
HM: I’m obsessed with a jazz pianist, named Bill Evans, and I’m trying to learn his style. The other interest is photography. Unfortunately, I don’t have a dark room, so I’m just taking pictures, but I have a beautiful collection and spend a fair amount of time looking at the latest photography that’s out there.

CT: Do you have a focus for your photography?
HM: I take mainly black and white, and it can be landscape, people or abstract art. The issue is how light and shadow interplay. Most of what I do is more in the landscape field and particular objects like trying to imitate Edward Weston and his photography of vegetables, the most famous being a green pepper. I just bought a photograph I saw in Munich, which I thought was the most beautiful portrayal of the intensity of depression and loneliness. Most of the photography I have doesn’t have that morbid theme. It’s more landscapes from Weston and other photographers; so we don’t have much wall space left in our house.

CT: Do you have any advice for young scientists?
HM: This is going to sound strange; don’t go into the most crowded field there is, or if you do, find your own niche. Be creative in approaching things in a unique way. As I said about the NARSAD application pool, half of the clinical research people right now are in genetics and in brain imaging. So why be, a brain imager when psychopharmacology and biological psychiatry, that don’t involve imaging, have so much promise?

CT: Unless you want to say any more, I think we’re done.

HM: OK
ALFRED PLETSCHER

Interviewed by Andrea Tone
Paris, France, June 22, 2004

AT: We’re at the CINP Congress in Paris. It is June 2004. My name is Andrea Tone and I’m here this afternoon to interview Alfred Pletscher for the Archives of the American College of Neuropsychopharmacology. Why don’t you start by telling us a little bit about how you got interested in psychopharmacology?

AP: Well, that’s a complicated story. I didn’t start my career in psychopharmacology. I worked as a medical doctor, but, then, I became interested in research and decided to study organic chemistry; I thought it would help me understand how the organism works. I started to study organic chemistry in Zurich with the Nobel Laureate, Paul Karrer. That’s how I got into research. But I didn’t start my research with psychopharmacology. I started it on the metabolic side, studying carbohydrates and sugar metabolism in diabetes. Then, I got an offer from Hoffman-LaRoche, a large Swiss pharmaceutical company, to lead their biological research.

AT: Tell us about what was going on in Hoffman-LaRoche at that time. What was the company known for and what were they asking you to do?

AP: They synthesized and analyzed vitamins; they had almost all the well-known vitamins on the market. They were also involved in other pharmaceuticals, for example they had a new sulpha drug at the time I joined them. I accepted the offer but before starting my job I wanted to go to America to work in one of the famous research institutes there. It was 1954 and in Europe, including Switzerland, we were behind America in those years. It was the post-war period and our research was not at the same level. I was fortunate to be accepted at the National Institutes of Health in Bethesda, Maryland. It was a big clinical center, built in 1950, that had just opened. I was working in the laboratory of a very famous person, Dr. Bernard Steve Brodie. Although he was located in the National Heart Institute, his research was not focused on the cardiovascular system but on the brain, and psychopharmacology. In Switzerland he would have been obliged to conduct his research in one field, but in America the situation was more flexible. At the time of my arrival Brodie and his postdoctoral student, Parkhurst Shore had just found indirect evidence that reserpine, used at the time in the treatment of schizophrenia, might act on serotonin, in the brain.

AT: Do you think many of those early discoveries came about simply by accident?
Many discoveries come by serendipity but in this case the indirect evidence was based on sophisticated experiments. At that time people had no idea of what causes depression, euphoria, or anxiety, and nobody knew anything about the mechanism of action for psychotropic drugs. It was from indirect evidence in these and other experiments that it was suspected there might be a chemical in the brain behind pathologies like depression that was acted on by a drug. It might be! This was a very revolutionary idea. Many psychiatrists in those days said that was mere speculation. So, I was given the task to provide direct proof that reserpine releases serotonin, in the brain.

Did your company want you to do that? Were they aware of the importance of the research?

Hoffman-LaRoche was located in Nutley, New Jersey and I was in Bethesda. There was no biochemical method available for the detection of serotonin in those days so my first task was to develop a chemical method that could do that. I worked first in the gastrointestinal tract because it was known that the greatest amount of serotonin occurred in the gut. It was present in a ten times higher amount than in the brain. After I worked out the method, I started experiments with rabbits, injecting them with reserpine. What I found was that the serotonin content, measured in the morning, went down.

How did you measure the serotonin content?

It was a colorimetric method, primitive, but specific. I had to show this occurred, not only in the gut, but also in the brain. So, I had to work out a method that was three times more sensitive than the one I used before. This was the time a highly sensitive spectrophotofluorimeter, constructed by Bowman, Caulfield and Udenfriend in another laboratory of NIH, became available so I could use it first in my experiments.

Were you still in Bethesda doing these experiments?

I was at the National Institutes of Health with Brodie, and under his guidance I was doing these experiments. Parkhurst Shore helped me, but I was doing the research myself. I found, with this new instrument, that after reserpine the serotonin in the hypothalamus disappeared. Parallel to the decrease we noted that the animals became sedated. Then, after repletion of the serotonin stores in the hypothalamus, the behavior of the animals normalized. The reserpine-induced behavioral changes were immediately tied to changes in the level of serotonin. If there was no serotonin, there was sedation. If there was enough serotonin, the animals were normal. Later on, it was found by others that reserpine depleted other neurotransmitters, like noradrenalin and dopamine. It was Arvid Carlsson in Goteborg, who discovered that reserpine depletes the other
monoamine neurotransmitters. Our findings indicated that at least the action of one psychotropic drug was mediated by a chemical neurotransmitter in the brain.

AT: It provided an empirical foundation for the development of psychopharmacology.

AP: Yes, it was one of the important findings that provided a basis for development of the field. At the same time Hoffman-LaRoche had a drug, called, iproniazid that was to become the first of a series of antidepressants referred to as monoamine oxidase inhibitors. Iproniazid is an inhibitor of the enzyme, monoamine oxidase that is important for the metabolism of the neurotransmitters, serotonin, norepinephrine and dopamine, in the brain. It was Albert Zeller at Northwestern University in Chicago, who found that iproniazid caused inhibition of monoamine oxidase. Almost at the same time Nathan Kline, the head of a Psychiatric Institute in New York State, recognized the drug had a favorable effect in patients with depression. It was the first evidence that a MAO inhibitor was effective in depression. As an employee of Hoffman-LaRoche, working at the National Institutes of Health, I took iproniazid and injected it into rabbits. What did I see? Serotonin levels instead of going down, as with reserpine, went up. Then, when I injected iproniazid before reserpine, the serotonin-decrease was antagonized. So I could say the antidepressant effect of iproniazid was possibly mediated by the neurotransmitter serotonin. This defined our theory that psychotropic drugs did not produce their psychological effect out of the blue, but had a biochemical basis. I played a role in that I did the initial experiments, which brought proof that the psychotropic effect of reserpine is mediated by a neurotransmitter, and I provided experimental evidence with iproniazid that the theory regarding the role of neurotransmitters in psychotropic effects was right.

AT: How involved was the company at this point in the development of an antidepressant? Was there even a market for them?

AP: They started to market iproniazid, the first monoamine oxidase inhibitor antidepressant and the sales went up very, very well. Then, all of a sudden, there was a drop in sales. What happened was that a patient in California, who had taken iproniazid, got liver necrosis and was transferred to New York where they made a big story out of it. My wife and I were riding in a bus from New York City to Montclair on a Saturday afternoon, and in front of us was a guy reading the New York Times. I sneaked a peak at the headlines over his shoulder that said: Inspectors Come to City to Ban Deadly Drug. I also saw it was iproniazid; my drug. Later on I heard of other cases of liver damage but although iproniazid was taken
off the market other monoamine oxidase inhibitors continued to sell quite well. So they must have been good drugs for the treatment of depression.

AT: Do you think the condemnation of the drug was exaggerated?

AP: All public outcries are probably exaggerated by the media. They exaggerate to attract attention. It was certainly something unique that happened. One, of course, has to be very cautious with MAO inhibitors. But, as you know, there are two types of monoamine oxidase enzymes; nowadays we have inhibitors which act more specifically on the Type A and others which act more on the Type B enzyme. That can mitigate some of the side effects.

AT: When Hoffman-LaRoche put the drug on the market, did they do so with the expectation that there would be a large demand for antidepressants?

AP: Of course.

AT: Some historians have argued that in the 1950’s, it was anxiety, rather than depression that sold the drugs. Hoffman LaRoche would later be best known for benzodiazepines in anxiety. Were they confident in the 1950s about the marketability of an antidepressant?

AP: Yes, of course. Thousands of people have been in psychiatric hospitals for depression. And depression can be stubborn in responding to treatment. It was foreseen antidepressants might have a big market and in the beginning, the sales of iproniazid were very good.

AT: In hospitalized patients or outpatients?

AP: For hospitalized patients first. But, then it was marketed for outpatients, and used in general practice.

AT: Do you remember how it was marketed?

AP: It was called Marsilid; that was the trade name of iproniazid.

AT: You stayed with Hoffman-LaRoche until when?


AT: Tell me about what you did with the company for the rest of the time.

AP: I was in charge of biological research and then of worldwide research. When I returned from the National Institutes of Health to start my job with Hoffman-LaRoche in Basel I told top management that the primary area of research must be psychotropic drugs because that was the upcoming field. So, in chemistry and biology, on both sides of the ocean, research for many years was focused on the development of psychotropic drugs.

AT: Was that a hard sell or were they receptive to the idea?

AP: They were receptive. They believed me and saw there might be a growing market for psychotropic drugs. Then the fortunate discoveries of chlordiazepoxide (Librium), and diazepam (Valium) came. That is a nice story, too. There was a chemist, Leo Sternbach in Nutley, who came
from Poland and, as a postgraduate student, synthesized several hep- 
toxydiazapines in the 1930s. Then, in the early 1950s, while working with 
the company he synthesized more of these seven-ring compounds but 
it seemed nothing was coming out of it because the compounds were 
biologically inactive. The project was about to be abandoned but one of 
the last compounds synthesized he gave to the biologists to see whether 
there was something in it. Fortunately, the biologist injected the com-
 pound into rats and cats and found it produced sedation without sleep. 
While the known sedative drugs at the time, like phenobarbital, caused 
sleep and sleepiness in higher doses, this drug, that was to become know 
as chlordiazepoxide, was causnig sedation without producing sleep. I 
remember a demonstration by the pharmacologist that after injecting it to 
a colony of very violent cats they became pussycats. They went around 
your legs, purred and were very nice, but most importantly they didn’t 
sleep. That was very interesting.

AT: Hoffman-LaRoche was pursuing the development of psychotropics 
because, in the 1960’s, when Librium was approved by the FDA, mep-
robamate (Miltown, Equanil), was consumed by 1 in 6 Americans. Was 
the company involved in directing researchers toward lucrative paths, or 
was it the scientists, like you, who were saying we need to work on psy-
chotropic medicines?

AP: They were scientists in top management like me who believed that psy-
chotropic drugs were the future. So, the question was what type of 
psychotropic drugs? We were already into monoamine oxidase inhibi-
tors. We pursued our research with MAOIs mainly in Basel, although we 
did some work in that area in Nutley. In Nutley they had the facilities to 
screen for psychotropic drugs. The discovery of the unique properties 
of Librium was a serendipitous finding in biological testing. Sternbach 
knew he synthesized an interesting new compound but he didn’t know 
whether the drug had biological action. The biologists who discovered 
Librium has a novel pharmacological action stimulated Sternbach to syn-
thesize analogues. Some of these were found to have advantages over 
the parent substance and were also developed for clinical use. Another 
interesting aspect of the Librium story is related to my appointment in 
1958 as Scientific Director to reorganize the Research Institute in Nutley. 
At the time of my arrival some of the early pharmacological research with 
Librium was already done and the pharmacologists were very interested 
in developing the substance clinically whereas the management was not. 
When I told management we had a compound that causes sedation, the 
response of both the president and the research director was that we 
needed a strong hypnotic and not a weak sedative. But, regardless of the
opinion of management, we moved ahead with clinical trials with Librium. The success was enormous from the beginning.

AT: That’s very interesting. They were more interested in a hypnotic than in an anxiolytic?

AP: Yes. An important part of the story is that Librium was developed clinically because we pushed it in spite of lack of interest by management.

AT: Let me, ask a couple of questions and, then, I’ll invite you to say anything you would like to add. You said in the piece you did for the final volume of the CINP collection, that when you went into industry, you had misgivings about what working for a company might offer versus working independently. Looking back on your career, do you still have any misgivings about working for industry?

AP: No, I don’t have any misgivings at all. If you decide to go to work for industry you have to make some compromises. One is that you have to pay for research from money you generate from your success. So you cannot work on all the different drugs you are interested in. You have to work on drugs that have a big market to generate money. But you can do wonderful research in the pharmaceutical industry, much more than at a university or in public and state institutions. At Hoffman-LaRoche, we had an especially good situation. We could do almost everything we wanted. We were free in our research, but we were expected to have in the back of our minds that we had to bring in money to do what we wanted to do. This was the reason I did not pursue my interest in developing drugs against malaria or tropical sleepiness and decided we should work on the development of drugs for the treatment of depression and schizophrenia.

AT: Within those boundaries you felt you had a lot of flexibility?

AP: I had a lot of freedom, and I was happy. But I don’t know how it is nowadays. If they had prevented me from doing my work to develop a drug that was seen by management as a weak sedative, or to develop psychotropic drugs in general, I would have left. But remember, in spite of the lack of interest by top management in a “weak sedative”, as Librium was perceived, we were able develop it.

AT: It’s a good thing you advocated it.

AP: Yes.

AT: What was your most significant contribution to psychopharmacology?

AP: My success in developing therapeutically effective psychotropic drugs. When I joined Hoffman-LaRoche the company had a sulfa drug, Gantrisin that had yearly sales amounting to six million dollars. But when Librium was introduced it had yearly sales of almost a hundred times that volume.

AT: Is there anything that you would like to add to this interview?
AP: Well, I had another interest in which I invested much time. I was looking for a peripheral model of serotonin release and uptake in humans. Working in this area of research in collaboration with the National Institute of Health we found that blood platelets have similar mechanisms for the release and uptake of serotonin as the central nervous system.

AT: Thank you very much for a wonderful interview.

AP: My delight.
GERALD J. SARWER-FONER

Interviewed by Joel Braslow
San Juan, Puerto Rico, December 9, 2003

JB: I’m Joel Braslow, and I am interviewing Gerald Sarwer-Foner. We are at the ACNP meeting on December 9th, 2003. Tell us something about your background and how you got into our field.

GS: It’s a funny story. I went to the University of Montreal Medical School because it was cheaper and more accessible for me than going out of town. I was introduced by an acquaintance to Father Mayo, a Dominican priest, head of the psychology department and analytically trained. Father Mayo and I became very good friends. So, four years later, after graduating and finishing my internship, he suggested I apply for residency in psychiatry at Butler Hospital, in Providence. I had never heard of Butler Hospital which is one of a chain Dorothea Lynn Dix inspired hospitals from 1814. It was built in 1826 for very wealthy people who would come with their cooks and their butlers.

JB: When was this?
GS: I graduated in 1950, so it was in 1951.

JB: Where did you do your residency?
GS: Butler Hospital and Western Reserve for the first two years. Then I came back to Montreal for the last two years because McGill demanded four years to get a diploma in psychiatry. I was chief resident at the Queen Mary Veteran’s Hospital for two years.

JB: Tell us something about Butler Hospital and your residency.
GS: It was a beautifully organized place. There was plenty of staff and wonderful nurses. Today, Butler is the center of psychiatry for Brown University School of Medicine, but at the time Brown didn’t have a school of medicine. The clinical director was a psychoanalyst and Gregory Zilberg, a psychoanalyst came up from New York regularly and taught us. We got very well trained; it wasn’t the dark-ages. In 1944 George Alexander was medical superintendent, did some work on ECT and left a tradition of differentiating between different forms of psychotic depression. To this day, when I teach students about depression, I start with the varieties of psychotic depression, which you see very rarely nowadays, but they’re there. George Alexander also taught that if the patient with psychotic depression did not get better within thirty days you could not be sure if the patient got better because of treatment or because of spontaneous remission and the natural history of the disorder. At the end of the first year, there would be about 15% still depressed, and in the second year half of that would recover. So, about 7% became chronic depressed patients. He
obtained these figures from British epidemiologists. When I was there we had one doctor for about 10 to 12 patients and used all the available somatic therapies including insulin coma.

JB: When you first started psychiatry did you see yourself more psychodynamic or biologically oriented?

GS: I had nothing against biology, but we were taught how you deal with a human being. You talk to them and you try to understand them. Freudian concepts came into it right away.

JB: Did you do psychotherapy?

GS: I did; they taught us about transference phenomena and so on. So, yes, I was psychoanalytically trained and became a psychoanalyst and a training analyst.

JB: So how did you become involved in psychopharmacology?

GS: I’m also one of the pioneer psychopharmacologists. At Butler I had seen what very well-staffed, properly-trained doctors can do with intimate contact with the patients. After I went back to McGill in 1953 psychopharmacology had just started in the New York State Department.

JB: On the eve of when Heinz Lehmann published about chlorpromazine?

GS: Yes, but I became involved even earlier. I’d gone to a French university and as a student I started an undergraduate medical journal in which we reviewed prominent articles from medical journals. So in 1947 I had read Henri Laborit’s papers.

JB: On promethazine?

GS: That’s right. Promethazine was an earlier version of chlorpromazine. Henri Laborit, a naval surgeon who was also an anesthetist, was operating on brain tumors, including vascular gliomas. To calm the patients he used what he called a “lytic cocktail”, which included promethazine. He noticed that patients given promethazine were very quiet. Later he also tried chlorpromazine. He told someone what he observed and the information got to Pierre Deniker. Now Deniker and I were friends until he died.

JB: You were friends with Deniker?

GS: Oh, intimate friends.

JB: What kind of person was he?

GS: A wonderful fellow. I’m still in correspondence with his wife. Anyway, Deniker worked with Jean Delay, who was something of a French aristocrat, even though he didn’t come from an aristocratic background. I also knew Jean Delay very well. In fact, I was his interpreter and guide when he was president of CINP. Delay worked with Pichot, a psychiatrist, also a good friend, Thuillier, a chemist, and Deniker. Deniker was a Huguenot, a French protestant. His father had been made a representative to China, and the family had lived in China. Most of his brothers and sisters died
there. Pierre was a remarkable guy and a very solid, decent human being. He was in charge of the clinical work. They took 38 manic-depressive and agitated patients at St. Anne’s Hospital, and administered them chlorpromazine. Their first paper on chlorpromazine was based on the findings in these patients. Now, afterwards, there was a little bit of bitterness; Laborit felt he wasn’t getting full credit. But it was Deniker who published the first series of papers, not Laborit.

JB: So you first became aware of Laborit in about 1947 when you were doing this medical student journal?

GS: Yes. When I met Laborit at a meeting in France, and said, I loved your papers, he replied, “You read them? Nobody has read those”.

JB: Did you appreciate the significance of what he was saying about promethazine?

GS: No, but it was interesting that it would keep people quiet.

JB: Did you see it as another barbiturate when you first read about it?

GS: It could have been. I just read it. It was very interesting.

JB: So when did your interest in psychopharmacology start?

GS: When Nathan Kline published the first papers on reserpine. In fact, Kline and I became good friends. We started to use reserpine together with psychotherapy from very early on. At Queen Mary Veteran’s Hospital, I had one doctor for five patients. We had a nurse for every two patients. I could put eight people to observe each patient. We published that some patients got worse if the drug broke through their major ego defenses, instead of supporting the ego. This became my contribution.

JB: Could you give an example?

GS: We had a Canadian army officer who had been a sergeant. As a sergeant he had been able to sit around with the boys. When he became a junior officer he wasn’t particularly welcome in the mess and began to drink too much. He showed anxiety, and they brought him in. Since he was very anxious and agitated we gave him reserpine. Suddenly he felt tired and weak and started to complain that his left arm and leg was getting blue and big. I saw the state he was in and realized that activity equals masculinity and cutting out the activity equals femininity; he was going crazy when his activity was cut down by reserpine. So very gently, we got him off the drug and pointed these things out to him. Four or five days later he was his usual self and we discharged him back to the army. He never had any further break as far as I know. This was a direct influence of suddenly feeling weak and tired. His feminine side came out and there it was. We published a paper on 14 people who were made worse with chlorpromazine and reserpine. As we went along, I felt these drugs were not, in essence, curative, but they could be used for their pharmacological...
action. If chlorpromazine made you tired or weak it was going to be good for agitated patients as Deniker had already demonstrated. If a drug gave you more energy, and made you outgoing, this had to be good for somebody who felt weak, tired, helpless or exhausted, as certain obsessionals or depressives. In the beginning, we deliberately picked people whose disorder of emotion or affect was so clear that it could be decided before they got any medicine. And then we prescribed them the most appropriate drug, depending on what we were trying to achieve. Obviously, we didn’t always achieve what we wanted to. We also learned the limits of drug therapy because we weren’t looking for total cures. But we got total cures in some cases, very quickly. Why did we get total cures? We get total cures, if the drug controlled the symptoms, which represented what the patient couldn’t handle at that moment. In these patients the drug started them on the way to cure. So how did the patient test that? The patient tested significant others in the environment, nurses and his family, to see if they think that they improved. If they confirmed it was so, the patient got better. In essence, I didn’t feel these drugs would necessarily produce a cure.

JB: Was that a commonly shared view?
GS: No, not at all.
JB: Heinz Lehmann didn’t think that?
GS: He shared that with me.
JB: He shared that with you?
GS: Yes, he shared that with me. He didn’t say this, but he agreed with me. In the early years the community of psychopharmacologists was very small and the few of us knew each other. We started to meet regularly, at least, at the beginning. The New York Academy of Sciences put on a session in early 1954 or 1955 and they invited everybody who had done work in the field including myself. I was one of the speakers. Of course, Kline had produced reserpine, so he was there. That’s how I got to meet him for the first time. And Hi Denber was there. Then, a crucial thing happened in New York which didn’t happen anywhere else. The New York state system, the largest psychiatric hospital system in the world at that time, appointed Henry Brill as one of the assistant commissioners to set up a psychiatric research unit to do psychopharmacology research in the different hospitals. Denber set up a unit at Manhattan State Hospital and Sid Merlis took Pilgrim Hospital, which was the largest with about 12,000-beds at the time. And that was the beginning of psychopharmacology. The psychiatrists in state hospitals believed that these drugs, reserpine and chlorpromazine, were antipsychotic drugs.
JB: But that term wasn't commonly used at that moment. Were they actually using that term?

GS: Yes. I said, they shouldn't be called antipsychotics. They should be called symptomatic drugs which do different things. Then Fritz Freyhan gave the term target symptom approach to how I was using these drugs. Fritz, a German Jew from a wealthy background and a great psychiatrist, was the superintendent of the only state hospital in Delaware.

JB: Was he the first use of the term, target symptom approach?

GS: Yes. My work started in 1954 and my first papers came out in 1955. In 1957 he coined the term. I organized a meeting in Montreal on the lines of Royal Society meetings with small committees of five or six people and each committee discussed specific papers with 25 to 50 people sitting in a room. There was a full hour for discussion and all presentations and discussions were tape recorded. The transcripts from that meeting became my book, *The Dynamics of Psychiatric Drug Therapy*. At the beginning, Cameron, the Head of the Department of Psychiatry at McGill, didn’t like the idea, but when he saw what I did he wrote the Preface. And it’s a great big book; full of all sorts of ideas, not just mine. We kept every bit of discussion by all the people. There are some marvelous ideas about LSD and all sorts of research ideas. What was important that we encouraged maximum discussion! We allowed people to kick ideas around, recorded them and published it verbatim. Because of that I was well known in the early years of psychopharmacology. My approach was to look at each patient; we had to have enough time to study them individually. We only gave them drugs when drugs when needed. And patients always got psychotherapy around what their problem was. And I still teach this today. Now, it's a very, very minority view, because people don’t know how to do it and nobody is teaching the psychotherapy part. I was invited by the Japanese to give a lecture on psychotherapy of psychotic patients. So, I teach whatever is needed. We don’t teach about depression any longer. They call it disorder of mood. What is a disorder of mood?

JB: What you’re describing is a narrowing of vision.

GS: Now the DSM-III and DSM-IV are set up to guarantee a consensus, so patients have an accurate diagnosis. I have no problem with that. But they changed the vocabulary. It’s now a mood disorder. Well, there’s a mood disorder aspect to be sure. But what do you do with a person who’s in a depressive stupor? What do you do about the guy who says I’m a zombie, I have no brain, I have no heart?

JB: It isn’t in our language anymore.

GS: I know, but the cases are there.

JB: Do you think that DSM-III had a major effect on the language of psychiatry?
GS: It is not just the DSM-III but the pressure from pharmaceutical firms. They're not out to cheat anybody, but they are interested in saying, here is a drug which has certain effects. You have to see what the drug does to the patient. Sometimes it makes them worse; often it makes patients better. So you have to organize things to accomplish that. You and the patient work together; I do this all the time. Most people don’t.

JB: Do you think that your approach was often used in the mid to late 1950s?

GS: It was a minority approach, but people who knew about it respected it. I received every honor in psychopharmacology.

JB: You would think your approach might have been fairly standard in those years?

GS: It was and it wasn’t. First of all, a lot of people weren’t trained to a level where they were comfortable working with ego defenses in psychotic patients. I was. My analysts, and especially one of them, Clifford Scott, did a lot of this work in England, so I had some guidance. Interestingly enough, when I was an analytic student, the New York Psychoanalytic Institute, the holy of the holies, invited me to give them lectures, on the use of drugs in psychotic emergencies. I talked about what the drugs would do, how they could be used and how analysts could analyze the psychotic transference using them. I was lecturing there for about two and a half years. By then they didn’t need me anymore because I wasn’t the only one teaching that approach. They had people in New York to do it. The famous Mort Ostow entered the scene, who first presented his ideas at the meeting I had in Montreal. He was bright as hell, an encephalographer and neurologist before he became a psychiatrist and psychoanalyst. So he had a good scientific background. Azima, too, had a good background. There were several of us involved in a psychodynamic approach to psychopharmacology.

JB: Where was Azima?

GS: Azima was at the Allan Memorial Institute in Montreal. If Lehmann’s paper on chlorpromazine hadn’t been published, his paper would have been the first North American paper on the drug. He published three months after Lehmann; it was a very good paper. There were others working with chlorpromazine at the same time, like Winkleman, a psychoanalyst. He had the drugs first in the United States, but he didn’t publish his findings on time. Bill Winkleman’s father was a famous neurologist in Pennsylvania and they had a clinic for psychiatric patients.

JB: You were in Montreal for how long before you left for Wayne State?

GS: No, I went from Montreal to become chairman of the Department of Psychiatry at the University of Ottawa. Then I moved to Wayne State University. I do a lot of teaching and plan to continue.
JB: Over the course of your career what do you consider your most important contributions?

GS: My papers on schizophrenia, manic-depressive illness and character structure. A lot of this is in book chapters.

JB: Over the course of your career you’ve remained fairly close to your psychoanalytic roots. I imagine there are not too many psychoanalysts, especially practicing psychoanalysts, now in the ACNP.

GS: When ACNP started, I was a Charter Fellow, and I’m one of the rare Life Fellows now.

JB: Often you hear there is a big rift between psychoanalytic and biological approaches. Do you think in the 1950s and early 1960s there wasn’t nearly as big a rift as subsequently, or was the rift always there?

GS: The rift was there, but there were and are reasonable people on both sides.

JB: Did that get worse over the years?

GS: It’s when some people demonize the other side that the trouble starts.

JB: What have you been doing recently?

GS: I’m teaching at Wayne State; Windsor is right across the river from Detroit. They have 10 psychiatrists for 300,000 people. I give them two days a week. The patients only get 10 minutes when they see a psychiatrist and drugs. I’m the only one that gives them 45 minutes. I’m not there as a psychoanalyst, but I do deal with psychotic and neurotic defenses. Nobody teaches about ego defenses any longer. They don’t even use the term; it’s nonexistent in the current terminology of psychiatry. That’s ridiculous! What do they think the patients are doing with their delusions, with their actions? These are defenses. These are ways to fend things off; it allows them to feel better. I also lecture all over the world, including France and Germany. I speak both languages.

JB: We’re going to have to stop. Are there things we haven’t covered?

GS: If you agree, I’ll send you a whole slew of my papers. Call me if you have questions.

JB: I would love that. Thank You.
This will be an interview with George Simpson for the Archives of the American College of Neuropsychopharmacology. We are at Tulane University in New Orleans. It is May 9, 2001. I am Thomas Ban. We should start at the beginning; where and when were you born and could you say something about your education?

I was born in Pennsylvania, which surprises a lot of people. My family came to America after World War I and my father worked as an electrician in the coal mines. My brother and I were born in the US. When I was two and a half, my father died. Soon after, I went back to Scotland and grew up in a small town in Lanarkshire. I went to school there, then, junior high five miles away, and finally I went to Glasgow University and studied biochemistry. I volunteered to enlist in the air force but they deferred me because the war was coming to an end. This was 1944, so I stayed and graduated. They didn’t have an organized course in biochemistry, so what I did was physiology and chemistry. I was a terrible student in the sense I had a lot of fun and a lengthy adolescence. After graduation I had to do work of national importance. They sent me to work with Distillers in Liverpool, who made Scotch whisky and antibiotics; I was unlucky enough to get the antibiotics. I worked there for two years; it was interesting and I enjoyed it. It paid well so I applied to college and stayed another two years, working in the summer for ten weeks with Distillers, which helped financially.

When did this happen?

From 1948 to 1950. I started medical school in 1950. I was a good student, I liked medicine and I studied harder. I finished in 1955 and did a compulsory year internship, six months in medicine, which included neurology, and six months in surgery. Then I applied for a Fellowship in France. I was short listed and when I was interviewed and asked why I wanted to go to France, I waffled and told them because I was going to do pathology. The interviewer looked at me and said, “Which country in the world do you think produces the most pathologists per head of population?” When I said, Scotland, he replied, “So why would you want to come to France?” After that I was reading the Lancet and saw an ad from McGill for applicants in their psychiatry training program. I wrote a letter in long hand and received a cable from Ewen Cameron accepting me. He’d never seen or met me before!

So, you moved from pathology to psychiatry?
GS: Pathology was just a reason to spend a year in France. I had been interested in pediatrics and psychiatry and eventually decided I’d rather do psychiatry. The department at Liverpool wasn’t that good. Frank Fish was the first Chair, but he came later. They had only a Reader at the time so I thought of going to London, but instead chose Montreal.

TB: Could you tell us something about the training program at McGill?

GA: I thought at the time it was good. In retrospect, I think it was superb; it was probably the most eclectic program that has ever existed.

TB: Tell us something about the faculty in the department of psychiatry.

GA: Eleven to thirteen people there at the time became Chairs of Psychiatry. Charlie Shagass was doing sedation threshold work predicting the outcome in depression. Bob Cleghorn, who succeeded Cameron, and Bruce Sloan, who became chair in LA, were supervisors of mine as was Jim Tyhurst, Robin Hunter and Tom Boag, both became Chairs. Clifford Scott, who was president of the International psychoanalytic movement, was in the department. He was a nice man but I discovered it was difficult to understand what he was talking about. Azima was there and Prada, who was a pupil of Cajal, and Ted Sourkes, a biochemist. It was probably the only department in North America that had a steroid chemist and a catecholamine chemist within a department of psychiatry. Malmo was doing his work on galvanic skin response to measure anxiety. So it was interesting but a bit confusing for a young doctor; it made you read because it was very competitive. That was the first time in my life in medicine; I felt everybody knew more than I did. During the first three weeks I read from cover to cover Frieda Fromm-Reichmann’s Principles of Intensive Psychotherapy, Anna Freud’s The Ego and Mechanisms of Defense and Bleuler’s text on Schizophrenia. I studied the lingo so I could talk rubbish with the rest of them. And Cameron was a marvelous administrator, but a terrible researcher.

TB: Did you have any contact with Cameron?

GS: I was on Cameron’s service and he had a number of Scottish private patients he handed over to me. We used IV methamphetamine as a diagnostic test and people were giving LSD as the royal road to the unconscious. We were trying everything, even though, looking back, some of it was naïve. John Davis and Dave Janowsky wrote a paper on using methylphenidate, a dopamine agonist, as a diagnostic test in schizophrenia without realizing it was used as a routine at McGill twenty years before. We gave a lot of electroconvulsive therapy and we still used insulin in the treatment of schizophrenia. I found, afterwards, that I missed the Department at McGill. It was like a big family.
Several people in the Department were involved in psychopharmacology research at the time you were there.

Yes, Sarwer-Foner and Bruce Sloan were doing some work in psychopharmacology, and, of course, Heinz Lehmann was doing a lot.

So, Bruce Sloan was involved with psychopharmacology in those years?

Yes, and I don’t remember who, but someone was working with perphenazine. There was a room for sleep therapy, a treatment used in Russia extensively in those years, and a day hospital where ECT was used with anesthesia and muscle relaxants. When I went to New York they were giving ECT without any muscle relaxants or anesthetic; I couldn’t believe it! I was even lectured on how silly it was to use them.

Could you say something about Cameron himself?

Cameron was a very interesting man; he had two great young analysts, Robin Hunter and Tom Boag, and he put one in charge of ECT and the other in charge of insulin. It made them into all-round psychiatrists, and they were both terrific people. I told Heinz Lehmann I was disappointed I didn’t see more of him. He was really an all-rounder.

So, you were in contact with Heinz Lehmann?

Right. After what was a stimulating year I applied for every program in the States that took foreign medical graduates, was approved for three years and paid trainees $300.00 a month. Those were my criteria; I sent out about three dozen letters and a few days later Cleghorn told me he had a call from Nate Kline in New York. That was the only place I interviewed, because Nate invited me to Rockland State Hospital where he had a research group that was stimulating.

When did you move from Montreal to New York?

In 1957, when they were involved with reserpine and monoamine oxidase inhibitors. Nate had a big private practice where he put patients on new drugs to evaluate them. They were mostly uncontrolled studies, a complete waste of time, with small sample sizes, but I participated in one of them. In the only clinical paper that Brodie has his name on, he wrote that imipramine was demethylated and had alluded to animal models in which desmethylated imipramine acted as an antidepressant. Since it was a metabolite of imipramine he suggested it might act faster than the parent substance.

This was in 1962, wasn’t it?

That would be about right. I was co-author of the paper.

Did you find that desipramine did have a faster onset of action than imipramine?

You couldn’t tell, because in all depression studies, you get this big improvement in the first week. I’ve forgotten the sample size; it was
something like 22 patients, so there would be no way of knowing without having a control to arrive at that conclusion.

TB: What else were you involved in at the beginning?
GS: I ran a research ward; we were interested in the Gjessing Syndrome, so we had a couple of patients diagnosed as periodic catatonia.

TB: How did you diagnose patients with periodic catatonia?
GS: It was a clinical diagnosis but not a lot came out of that study.

TB: What else were you involved with?
GB: I wrote a grant for measuring endocrine status to predict outcome of drug treatment. Jonathan Cole said he thought it was a good idea, but we should expand it. I was too junior to be the project director so Nate became the principal investigator. Eventually we got a paper out of it, but I didn’t put my name on it because I felt there was nothing there. Then I collaborated with Ted Cranswick on a project about thyroid function that turned out to be a false lead because institutionalized patients were fed iodized salt. I also collaborated with John Blair, studying the semen of patients.

TB: Could you say something about the people at Rockland? Were Saunders and Barsa still there?
GS: Saunders was there and Barsa as well. Barsa and Saunders were originally working with Nate on reserpine until Saunders came along with the monoamine oxidase inhibitors. He had some notion that monoamine oxidase activity might be related to the effectiveness of those drugs. Saunders was not a psychiatrist, so they got some young doctors in the admission wards to treat patients and report back. I thought that was pretty awful. So I decided to get involved in treatment and did a study with Saunders on a butyrophenone, a Wyeth drug. After that I started working on my own, because it seemed to me that Saunders was having trouble with Nate. It was then that I applied for an ECDEU grant.

TB: You mentioned briefly that there were some problems between Saunders and Nate. Could you elaborate on that?
GS: It was about the introduction of MAOIs. They gave a paper on iproniazid on which Nate was one of the authors. Nate ran with it and publicized it, but after he got the Lasker Award, he wrote an article, I think it was in the American Journal of Psychiatry, claiming most of the credit and Saunders sued him. I think Nate was the right man in the right place to publicize it but he could have given more credit to the other authors of the paper. That suit went on for ages and, obviously, was disruptive. Saunders did eventually take residency training, but then moved out of the field altogether. Eventually Saunders won the case, but the judge, after all those years, gave them a third of the award’s ten thousand dollars. They must have had a fair amount of lawyer’s bills.
TB: What about Barsa?
GS: Barsa worked in a large building where, it’d be safe to say, there were at least 500 patients. He and another doctor took care of them all. It’s very hard to do research in a situation when one is looking after all the physical and psychiatric problems of so many patients. He did part of the reserpine study in that building, relying on casual observations. There is a story that they nearly missed the efficacy of reserpine. It was a hospital glazier who stated that at the time the study was done there were less cracked widows on the ward than ever before.
TB: Still, Nate Kline played a role in the introduction of both reserpine and iproniazid. Would you give credit to him?
GS: Yes, Nate deserved credit for the fact that his practice was strictly pharmacological. His practice was interesting; I used to cover for him when he went away, because he used to take six weeks of vacation mostly to attend the Salzburg music festival. When I covered for him, it was interesting to get many referrals from other psychiatrists and psychologists for his opinion. There were clinical trials done in the office, and we attempted to use controls but that was difficult because Nate liked to use a touch of this or that, from whatever was available at the time. In one of the studies, it could have been desipramine, Paddy Watts, who was working with us at that time, did the diagnosis, I did the rating and Nate did the treating but when I broke the code, Nate had added other drugs to half of the patients. It was in that office they did the endorphin study that got Nate into trouble.
TB: Wasn’t the endorphin research done much later?
GS: Much later, yes.
TB: Didn’t you do some research with histamine in schizophrenia in those years?
GS: That was done on Nate’s suggestion. Clearly, there was a difference in histamine sensitivity in schizophrenia compared to a matched group of organic patients.
TB: Didn’t you do some research on the effect of drugs on sexual behavior?
GS: That was done in the 1970’s. I treated one of my colleagues who got depressed with Nardil (phenelzine) and he awkwardly told me that he had been a control in clinical studies and measured his sperm count twice a week for the last couple of years. When he looked at the figures he saw that, after Nardil, volume, count, and motility went up. When his assistant got depressed and I treated him with Nardil, he was also a control and the same thing happened. Then, hard to believe there was a third person in the lab who got depressed. I felt I should write it up, and publish it as a letter. The subjects were three researchers, but Nate
wanted his name on this paper. Sometime later, there was a snippet in Time Magazine about somebody in Vermont who bought a magnificent and expensive Argentine bull which was producing no sperm and Nate was giving the bull Nardil. Later on I found out that the three researchers had been drinking heavily but had to get off alcohol before I gave them Nardil; their sperm count increased after they stopped drinking so it probably had nothing to do with Nardil. That was an interesting little diversion!

TB: Could you tell us how you got involved with ECDEU?
GS: That was after I had done my first drug study with Jack Saunders and met with Jonathan Cole. When I received my NIMH grant I also got another 40-bed ward. And I became involved with an interesting group of people; Don Gallant, Art Sugerman, Sid Merlis, Hy Denber and many others. The first meeting I attended was in Palo Alto with Leo Hollister. Probably at that time I knew every psychopharmacologist in the country. There was camaraderie, and a fair amount of fun.

TB: Did you participate in the ECDEU program from the beginning?
GS: These other people were involved before me, but it was early on. We worked sort of independently and it was left up to you, what you did and how you did it. You could have said it was a government intervention to make it easier for the pharmaceutical houses to develop drugs. It was one way of selecting a group of people who could study drugs better. Nearly all of these places were not in academia. Don Gallant and Leo Hollister had inpatient units. So did Sid Merlis and Hy Denber, but in state hospitals, as I was or in VA hospitals. So it was a marvelous productive idea that set the ball rolling. I feel it wouldn’t be a bad idea to bring it back because there is a concern about the objectivity of some of the assessments today. Today, they are talking about how pharmaceutical houses design the studies, their staffs manage the data, and clearly nobody is totally free of bias. By being totally independent and in control of the situation the ECDEU investigators could look at whatever drugs they were interested in. In the early 1960’s, I looked at Tegretol (carbamazepine) in schizophrenia before the drug even had a name. It produced the most unquoted paper I ever wrote but it was the first time Tegretol was given to psychiatric patients.

TB: When was that?
GS: I presented it at the CINP Congress in Birmingham in England, in 1964. I sent the paper to the British Journal of Psychiatry and they said, this drug will never be used, certainly not in Britain. I never sent it anywhere else so it was only published in the proceedings of the meeting. Actually it showed that you could convert people from multiple antiepileptic drugs
Nearly all the patients managed to be maintained on Tegretol alone rather than the two or three anticonvulsants beforehand. We also did dosing studies and looked at extrapyramidal symptoms (EPS). It was during the 1960’s that we developed a rating scale for EPS and I first published about that in 1964. All the antipsychotic drugs produced Parkinsonism and until then there wasn’t any scale for assessing it. We thought if you could quantify it, it would be easier to look at the potency of drugs relative to that side effect rather than psychopathology. So we developed the scale when Scott Angus was working with me. We also published a whole series of papers in 1970 on the scale. I never thought people would use it like they ended up doing. It was designed for use in inpatients. It was not to detect questionable EPS but to look for definitive EPS.

TB: That scale has certainly been used widely.

GS: We modified it a little, because not every outpatient clinic has a table or couch. With the new drugs most of these scales are probably not too helpful because there is very little EPS. It would be interesting to go back and look at handwriting that detects sub-clinical EPS, with the new drugs, like olanzapine. We did a lot of work on handwriting in the 1960’s. That showed that low dosages worked as well as high dosages.

TB: Could you tell us more about the handwriting test?

GS: Haase suggested that there was a very good correlation between minimal changes in handwriting and the therapeutic dose. He also suggested these minimal changes were sub-clinical; in other words you could see changes in the way somebody wrote long before you could detect changes in a patient’s gross or neurological status. Haase read them by inspection saying this is normal or abnormal. Clinicians did that very well with the EEG until it was quantified with the introduction of computers. Since no one did that with the handwriting we started to develop various ways of quantifying change. Then Phillip May developed an automated handwriting test and was going to send it to me, but he unfortunately died before he got around to it. I don’t know what happened to the handwriting test, it sort of dropped out of use. One problem was you couldn’t get every patient to write for you. But it was useful. By the time haloperidol reached these shores, Haase was saying that the therapeutic dose of Haldol was less than 5 milligrams. Current dopamine receptor occupancy PET studies suggest that 5 mg gives about an 80 percent blockade. So, I think we overdosed widely and to an extent harmfully, despite the handwriting data. If it had been easier to quantify we might have been able to convince people to use it.

TB: Could you tell us about the drugs you worked with in those years?
GS: We looked at a Wyeth drug that never got a name and we looked at trifluoperidol, both of which lowered cholesterol levels dramatically. Then, we looked at haloperidol and cholesterol levels; there was no effect. The FDA had asked for information on that. We validated our rating scale in the haloperidol study because we saw that 30 mg caused a lot of EPS compared to 6 mg. We studied thiothixene and loxapine before they came on the market. We did a study with a Pfizer drug that produced liver function abnormality and never made it, so not everything was marketed that we looked at. Finally, I think the pharmaceutical companies realized all of these drugs, from an efficacy point of view, were the same and that there were different side effects. So they needed a new kind of drug and the clinical response to clozapine stimulated interest.

TB: When did you work with clozapine?

GS: About 1974 first and we published a paper on its effect on tardive dyskinesia in 1978. It was interesting because the nurses on the ward knew immediately it was different. They saw improvement, a lot of sedation, a bit of hypotension, no EPS, improvement in TD, withdrawal effects and seizures. Seizures might be related to the high plasma level that these patients had but later I thought it might be related to the sudden increase in dose rather than in plasma level. One of the sudden increases was a suicide attempt and the other one an accidental double dose. We looked at metiapine, and that’s the only drug I felt absolutely convinced did something to a patient whom I have known for years that nothing had helped, including loxapine and clozapine, to which it’s related.

TB: What did it do?

GS: This was a patient who was a paranoid schizophrenic, who felt the Queen of England had visited him at Rockland and with metiapine all the delusions disappeared.

TB: What happened to the drug?

GS: They decided not to market it. I think it was the same Swiss company that had clozapine and loxapine. I suspect if there had been more of these kinds of cases, they would have pursued it.

TB: Could I ask you to say something about documentation of changes in general. We know that in the early 1960s it was very poor. When did that change?

GS: I think the ECDU was instrumental in changing it

TB: Could you elaborate on that?

GS: Eventually ECDU as a group decided we’d use the BPRS and the NOSIE in all studies. What that meant was you could compare studies. If you wanted to use other scales, that was fine, but these were the scales that went with the database. Out of that came ECDEU’s documentation
system in which Bill Guy was involved. He developed a series of forms that made it possible to use standardized documentation of a clinical trial with a number of rating scale prepared for optical scanning.

TB: Wasn’t Rockland State computerized rather early?

GS: They brought in a statistician, a young man, Gene Laska who worked with IBM, who set up a computer system and eventually everything was computerized. It was too far ahead of its time, the doctors hated it and the administrators loved it. At that time at Rockland, drugs could be rationed if there was a budget cut but I don’t think it ever happened. So every building had their private pharmacy in case they ran out of money. When the drug prescribing was computerized, you couldn’t order more than you required and the large inventory of drugs present at each buildings could no longer be increased for the hypothetical rainy day. Later every thing was on optical scan sheets and the computer produced a differential diagnosis an anamnesis and translated the numerical ratings into English words. In 1974 or 1975 I had an inpatient and outpatient unit where everything was computerized. We had a full drug history with all the information that could take weeks to find out, for example the reason for prescribing the drug, the reason for increasing of dose, the reason for addition of another drug as Cogentin (benztropine mesylate).

TB: Didn’t you have a specially developed mental status?

GS: Right. The first mental status was created by Paddy Harper, Gene Laska and me. Paddy was from Ireland and came to work with me. He did a lot of the work on developing the mental status and embedded a Hamilton Rating Scale and a Wing rating scale for schizophrenia in it. You completed the optical scan form, entered it into the computer and you received a printed sheet in reasonable English with rating score to the above scales. At the World Congress of Psychiatry in Madrid you could fill in the NOSIE in English and get the printout in six languages. I have a Russian publication on that. That was a lot of fun, it was helpful and I wish it would have lasted. Bob Spitzer came and worked on a second mental status examination with a narrative output and a marvelous storage system, but psychiatrists felt it was imposed from above and didn’t like it. We set up guidelines for prescribing, with the computer indicating that (1) this is okay, (2) do you really want to do that? (3) this is questionable; and (4) not permitted. That irritated a lot of people. I thought it would be good if people would know which drugs were best. Many psychiatrists prescribed haloperidol, which cost ten times more than fluphenazine, and nobody could differentiate between the effects of the two drugs. Gene Laska was very helpful. I’ll always regret that, when he wanted me to have a cathode ray tube on my desk in the early 1970’s, I said, Gene,
“Why should I have anything to do with computers when I can pick up a phone and call you”? With hindsight I should have done it; I would have been much better at working with computers than I am. It also helped us in our research. I can remember one time I did the last assessment in a project at 11:00 AM, and when I came back after lunch all the data were on my desk analyzed. Gene was involved in the first study which showed that you got withdrawal effects after stopping drugs but it was from stopping the anticholinergics and not the neuroleptics; the anticholinergics were the culprit. So, we did a controlled study. First we treated patients to produce a quantified amount of EPS using trifluoperazine; it took from 20 to 500 mg for different patients. Then, they were kept at this dose for an additional for weeks at which time they were abruptly withdrawn. We didn’t see anything! After the patients were drug free for four weeks they were treated in the same fashion to see if the side effect were the same in both occasions. After they reached the full dose and they were on this for a month we added benztropine mesylate for a month and when we withdrew both drugs, we got all sorts of problems. We also found that the anticholinergic drug sensitized patients for EPS. We followed that up in several studies. Then we did a three months dose response study with butaperazine after each patient were taken off drugs for a month and when they were put back on butaperazine, even on lower dosages, they had far more EPS than they had the first time. We didn’t measure blood levels. We did a lot of studies like that, filling gaps in our knowledge, which was fun.

TB: When did you start to do blood level determinations?
GS: Somewhere in the late 1960’s. There was a phenothiazine meeting and Irene Forrest gave an account of measuring phenothiazine metabolites in the urine. But most antipsychotics had many metabolites; I remember someone saying that chlorpromazine could have as many as 160 metabolites. So it was a nightmare. Then, we looked at butaperazine because we felt it might be easier to measure blood levels and we did some interesting studies. We also did blood level studies with loxapine and with lithium. But no one could ever show that measuring blood levels of antipsychotics was very helpful. Clozapine might be the only exception. Still, it had to be pursued because it was possible it could explain why some people respond whereas others don’t. I don’t think anybody measures blood levels any longer.

TB: Didn’t you measure lithium blood levels after a loading dose to predict response to treatment?
GS: Right. We had an MD from Sweden who was good at physics and mathematics and was modeling complicated kinetics of lithium after multiple
blood draws over a 24-hours period. They were then treated therapeutically with lithium. The laboratory technician phoned me and stated that this patient had the highest 24-hours blood level he had ever seen and questioned it. We then took another blood level even before he was at steady state which showed a very high lithium level. This led to us giving a loading dose of 600 mg with blood taking 24-hours later. Inspecting a table created from the raw data gave you an approximate dose required to approach a therapeutic range. It was useful particularly for outliers. The trouble was, you needed to measure lithium levels to the second decimal point and a lot of labs don’t even give you the second decimal point, some of the machines don’t read it. If you have a lab that does blood levels with the necessary precision it speeds up getting to steady state. We used a similar technique with loading doses to predict the amount needed to get into the therapeutic range with desipramine and nortriptyline. That would have been useful, but again, it never took off. We used it at Rockland and other people used it too. Tom Cooper, in the lab at Rockland, automated the techniques and developed methods for measuring, blood levels of antipsychotics, antidepressants and lithium. He did lithium levels using saliva and microamounts of blood from fingerpricks. So people like Gene Laska and Tom Cooper made life easier for me. We used lithium very early on in half gram capsules which we made up ourselves. I used to give everybody 1800 mg a day until we got a blood level and then we adjusted the dose. We didn’t really know what the therapeutic level was and we were shooting for about 2 meq./l. Surprisingly we did not get a lot of toxicity. We were probably just lucky.

TB: Let’s get back to chronology. Could you say something about your early studies with ECDEU?

GS: Power analysis didn’t exist so we did studies that were really under powered and even though we did some collaborative studies, the sample sizes still were not big compared to today’s samples. On the other hand in current study investigators and the sites are very heterogeneous, so you need to have large samples.

TB: Do you have any preference for single center or multi-center studies?

GS: We need them both. The kind of studies that were being done in those days would be hard to do today.

TB: For example?

GS: A dose escalation study. The doses, calculated from the animal data are helpful, but can be misleading. We found out a lot about drugs that way; but people would turn up their nose at that kind of study today saying the dosing information was contaminated by the fact you kept increasing it. It was not difficult for an ECDEU unit to do a study of 10 patients, and from
that tell a lot about a new drug. I remember a drug that I studied with 12 patients, and it was definitely active, but when we got liver function tests, they were higher than we would have liked and one patient had a seizure. We did a multi-center study at four sites in which Don Gallant and Art Sugerman were involved. In the larger sample there were three or four abnormal liver function tests and two seizures. We exposed less than 50 people to the drug and were able to say it was active but with too many side effects.

TB: Did you use the handwriting test in some of those studies?

GS: We did and, for instance, with clozapine we saw that handwriting increased in size, something we’d never seen before. With all other active drugs we got diminished handwriting area. Clozapine was an incredible advance in therapeutics as well as a huge incentive for research.

TB: Did your findings with the handwriting test correspond with the recommended dose?

GS: Yes, but what you saw was that, if you allowed doctor’s choice of dose, they might give up to 400 percent more than handwriting dictated. I always felt that, from a clinical point of view, it made sense to keep on increasing the dose until you got side effects, as long as you realized that by the very nature of that process, you would give more than you needed, and then you should back off. But people often didn’t do this and so we had a generation of high dose treatments that was not helpful.

TB: Didn’t you have a study designed for testing the correspondence between the dose based on handwriting test and clinical judgment?

GS: Eventually, we did a double blind controlled study, where I had one MD who trained with Haase who knew nothing about the patients but read their handwriting. He came one day a week. In that study, for half of the patients the dose was based on handwriting changes and in the other on the judgment of the psychiatrist. There was no difference in outcome but there was in dosage. Doctor’s choice was more than double compared to that of the handwriting group. The psychiatrist made the recommendation for the increase of dosage but if the patient had reached the handwriting threshold I did not write the order. In general psychiatrists tended to use high dosage in spite of the fact that there was never any evidence that higher dosages improve outcome.

TB: Weren’t you involved in testing drugs with an effect on methylation in schizophrenia?

GS: There was a drug for psoriasis with an effect on methylation and I tried to recruit several patients who had schizophrenia and psoriasis and sent them to the dermatologist in the hospital. But the dermatologist got so enthused about the project that instead of giving the drug orally, the way
he would normally, he decided he would give it in intramuscular form. Because we had to order it the hospital administration got worried about the study and it never happened. Various companies had drugs that inhibited methylation, but we didn’t have much to do with that.

TB: Didn’t you try antidepressants in schizophrenia?

GS: There was always a fear that if we gave antidepressants to schizophrenics it would over activate them. We had a group of patients with chronic schizophrenic who had been off drugs for a month and we gave them 300 mg of imipramine for a month but, apart from dry mouth, we didn’t see anything. I think Don Gallant gave even higher dosages in a study. We tried all of those things with the hope that one might have an effect. When I was an intern, in 1955 and 1956, I used chlorpromazine as a hypnotic, an antihistaminic, an antiemetic and an antipyretic as well as for hypotension, and for neurosis. It has some effect in all those conditions but, for all of them, there are better drugs available today.

TB: You said that you did some early studies with clozapine. Were you involved in studying any of the other atypical antipsychotics?

GS: Yes. Clozapine is a unique drug and it is still the best, but it is a difficult drug to use and not only because of the white cell monitoring. It’s a difficult drug to dose in that you can get hypotension and many other side effects. So we became interested in other atypicals. Risperidone was the first drug in that group; it was designed to affect the serotonin system as well as dopamine system. In fact it was the first designer drug in psychiatry. We studied it and found it a useful drug with good patient acceptability. That feature certainly helped atypical antipsychotics to advance. If you look at all the studies, it’s much easier to separate haloperidol from quetiapine and other atypicals by EPS than by psychopathology. The fact they produce less EPS is a distinct advantage and compliance issues should be better for the atypicals. So, after clozapine, we worked with risperidone. Then we did a little bit with quetiapine, and quite a lot with ziprasidone. We did work with olanzapine both in animals and in adolescents.

TB: Thioridazine, one of the first phenothiazine neuroleptics, produces less EPS than haloperidol. If my recollection is correct you did some research with thioridazine; didn’t you?

GS: In the 1970’s, there was an editorial in the BMJ, which said someone had been to a geriatric meeting and the only thing people from the UK and US agreed on was that thioridazine was the drug of choice for the elderly, which seemed to me a bit odd and wrong. So we studied a group of elderly patients with schizophrenia and an average of age 67, range from 60 to 81, who were off drugs for a month. Then under double-blind conditions,
they received either fluphenazine or thioridazine for eight weeks, then off medication for a month and then crossed them over to the other medication for another eight weeks. We saw more EPS with fluphenazine and more hypotension and weight gain with thioridazine. But the main finding was prolonged QT interval in 9 out of 30 patients on thioridazine and none on fluphenazine. Recently thioridazine got a black box warning from the FDA because of its prolonged QT. Our study was published in 1978. I stopped using thioridazine at that time. So, that study with thioridazine I thought was useful and clearly differentiated side effects between the drugs. The fact there was more EPS with fluphenazine validated the NIMH 1964 study that compared fluphenazine and thioridazine with chlorpromazine in which they saw more sedation with chlorpromazine and thioridazine but more EPS with fluphenazine. Fluphenazine and thioridazine were new drugs when that study was carried out. There was no difference in their effect on psychopathology which is true for all antipsychotics untill clozepin. That is a difference in side effects but not an efficacy.

TB: Wouldn’t that apply also to the atypicals in general?

GS: I think that’s true. The atypicals are, within limits, equal from an efficacy point of view. We have a poster at this meeting on our findings in a comparative study of ziprasidone and olanzapine. There was no difference in their effect on psychopathology but there was more weight gain with olanzapine. There was some indication of more EPS with ziprasidone. If you took somebody off haloperidol and gave them olanzapine or risperidone, you would be able to separate them on the basis of the EPS very quickly but it would be hard to show differences in efficacy. I think the CATIE study is useful, even though it’s very complicated, because you need an independent group of people to do such studies. At the annual meeting of the ACNP, a year ago, I commented that you don’t have to read the posters of these comparative studies of atypical antipsychotics. The sponsorship of the trial seems to dictate what the results are going to be. I don’t think people cheat, but they are unlikely to design a study that could go against what they’d like to see.

TB: Did Sy Fisher write something about that?

GS: Yes, he did.

TB: Didn’t you study the relationship between negative symptoms and EPS?

GS: The increase of negative symptoms paralleled the increase of EPS. We showed that there is a correlation between what’s rated as a negative symptom and EPS. So, if you don’t get any EPS you’re bound to be better on negative symptoms. My other thought is that akathisia could exacerbate positive symptoms and relate to poor outcome. Actually that was shown in our study with fluphenazine. Ted Van Putten wrote a lot
about that. Akathisia is very undesirable. If you have less akathisia and less rigidity the outcome is better. And don’t forget, you can not only get bradykinesia from these drugs, but also bradyphrenia, slowed thinking; the key question is, are there any differences between these drug-induced symptoms and primary negative symptoms? I doubt it.

TB: Is there really any difference in efficacy between the older antipsychotics and the newer atypicals?

GS: I really don’t know. John Davis just published the findings of his meta-analysis in the *British Medical Journal*. He gave me a copy yesterday, I haven’t read it yet, but he came to a different conclusion. But whatever his findings are clearly they represent an advance but how large of an advance remains unclear. The real problem is that people are struggling with their price. I have a concern because, in the United States, we’re soon going to feel that to use typical antipsychotics is malpractice, and that bothers me. I just got an e-mail from another university sending me a study that would compare long acting haloperidol and an atypical in the maintenance treatment of schizophrenia; the question was, is this ethical? To me, that’s strange, because you have one of the best treatments for maintenance and another that’s never been studied for that. My prediction would be that there would be more side effects in the haloperidol decanoate group but more hospitalizations or relapses on the atypical. So, I think we are throwing the older typicals out the window very quickly. I recently interviewed a patient who was on a study and he insisted that the best treatment he ever had was haloperidol. There’s going to be a handful of people who might very well prefer that.

TB: Do you think that all schizophrenic patients benefit more or less equally from treatment with antipsychotics?

GS: No. If you take John Davis’ meta-analysis you have 30 percent of people who are treatment resistant who improve with clozapine but if you look at risperidone it’d probably be about 15 percent. If you assume that 60 percent of people don’t do terribly well on typicals, and it might even be a bit higher over a long time, you’re still seeing a large number of patients who are not going to do all that well on atypical; there are no miracles. I’ve always had the suspicion that many people who did so well on clozapine were probably affective disorders. There’s always been the notion that a percentage of people with schizophrenia do not respond. It’s fascinating because, 20 or 30 years ago, if you gave a lecture and talked about taking people off neuroleptics, it would have been enthusiastically received. Now by many, it’s considered unethical. Clearly, if you have patients in a defect state or have a chronic illness whether you give them an antipsychotic drug or not, doesn’t make much difference. In fact, if you’re giving
them a drug that makes them over sedated, feel fuzzy or could give them some other side effects, they would feel better without it.

TB: Do you remember that in the early 1960s Frank Fish classified schizophrenic patients on the basis of Leonhard’s criteria and found different responsiveness in the different groups?

GS: Frank Fish came to Liverpool after I left. Clearly, Leonhard’s classification has had more impact with German and Continental psychiatrists. It’s certainly not the classification we use. Frank Fish was remarkable. He was a London Jew, who was a prisoner of war in Germany, learned German and became the English expert on German psychiatry. His book on *Schizophrenia* is very good. This classification would suggest probably 13 different sub-groups of chronic schizophrenia. I don’t know that anyone has looked at it in substantial numbers in terms of treatment outcome.

TB: Do you have any notion how we should proceed in this area of research to break the impasse?

GS: My notion would be that at least in some schizophrenic patients there are identifiable abnormalities at a very early age and that might be one group. Probably one of the best things for schizophrenia would be good obstetric care. In the 1930s about a third of people in Scotland were improperly nourished. Because of Rickets there were many women whose pelvis was too small to deliver children and the lower Cesarean sections hadn’t been introduced and there were many prolonged labors. One thing the war did in Britain was that, for the first time, the whole country was well nourished. This would result in fewer difficult labors in the future and the lower C section was introduced I believe in the 50’s. Then one would have to investigate what early interventions might do to outcome. In addition pharmacologists are looking at the NMDA receptors and other areas to find new drugs for schizophrenia. Dopamine blockade was a significant finding but it turned out to be slightly simplistic.

TB: So, you think we should be moving towards early detection and intervention?

GS: Yes.

TB: When you entered the field, chlorpromazine and reserpine were already used in schizophrenia. Wasn’t a butyrophenone the first drug you studied in schizophrenics?

GS: I’m not sure but I studied thiothixene, molindone, loxapine, clozapine, and a number of other drugs that never made it to clinical use.

TB: What was the last drug you studied?

GS: Ziprasidone and we’ve carried out several studies with it.

TB: Could you tell us about your findings?
GS: It differs in one respect from many of the other drugs; it doesn’t have as much of an effect on the histamine (H₁) system and you don’t get weight gain. And it is as good an antipsychotic as the others. This has to be seen against the background that more and more people are reporting weight gain and Type 2 diabetes with drugs like clozapine, olanzapine and quetiapine. In our six-week study on ziprazadone we had one woman who lost 18 pounds in six weeks. She had gained it on previous drugs. It’s not as if it’s a weight reduction drug, but that aspect was helpful. For the group as a whole there was a five and half pound mean weight difference at the end of six weeks and that is a lot. So, if you have somebody who is very overweight, you might give them ziprasidone. We looked at the drug in inpatients and outpatients and it was very acceptable to patients without a lot of troublesome side effects. The QTc prolongation present has been much exaggerated.

TB: What was the sample size of the study?

GS: This was a multicenter study, so there were a few hundred patients. In our own outpatient study we had 39 patients and at the end of six weeks, there was a significant reduction in cholesterol and triglycerides. The same was seen in the multicenter study that had about 260 patients, again there was a significant reduction in cholesterol and triglycerides compared to olanzapine.

TB: You were also involved in clinical investigations with antidepressants. You mentioned that in the early 1960s you studied desipramine.

GS: That was in the outpatient private practice of Nate Kline. There was one year we saw 400 new patients, the vast majority were seen by Nate himself. That is a very large number when you think of today and the difficulty of recruiting patients for depression studies. But there was nowhere else for them to go; most of them were or had seen a therapist and some had lengthy analysis. Albert Ellis and another psychotherapist referred patients and patients came looking for treatment; so it was much easier to do research. The trouble was we could do only a few controlled studies. You could argue that we did not use placebo but most of those patients had never used drugs before and you really did see people who made dramatic improvement and would tell us that they felt better than they had in years. They improved dramatically. I don’t think one sees anyone like that today because family doctors, gynecologists and internist are treating a lot of them.

TB: Weren’t you involved in research with MAOIs?

GS: Right, I still have an interest in them. There is a range of studies that show that people who failed to respond to tricyclics would respond to MAOIs.
TB: You worked with phenelzine and tranylcypromine, didn’t you? What about deprenyl?

GS: We never studied it definitively. It’s a Hungarian drug and I heard somebody is developing a patch giving L-deprenyl. That would be very interesting, because you could give a high dose.

TB: Did you work with SSRIs?

GS: I used them widely, but I never was involved in any clinical trials. I wouldn’t be surprised if venlafaxine is slightly superior to SSRI’s rather than the other way around.

TB: How do SSRIs in your opinion compare to imipramine or amitriptyline?

GS: There was an article in the BMJ not so long ago saying that when they looked at amitriptyline it was equal to or better than SSRI’s and there was a follow up article that suggested less self-harm with amitriptyline than with the SSRIs. There are many fascinating findings in the antidepressant field. Clearly the advantage of SSRIs is thought to be safety. There was a study from somewhere around Detroit in the mid 1950s claiming that isoniazid has antidepressant effects. Now, isoniazid is a similar structure to iproniazid but does not affect monoamine oxidase. That would be interesting to look at.

TB: The isoniazid findings would invalidate some of the neuropharmacological speculations. Were the findings followed up?

GS: No but they are still using isoniazid in tuberculosis; that is something one still could look at.

TB: It seems those findings were overlooked. I wonder why?

GS: Imagine taking a Marxist from Russia in Stalin’s days and trying to convince him that Marx was wrong. Data aren’t terribly important in belief systems, so that may be why those findings with isoniazid were overlooked. But, it’s certainly of historical interest. David Healy raised the issue and I spoke to him about it.

TB: David raised the issue in his book on the The Antidepressant Era.

GS: Yes

TB: The findings with reserpine and iproniazid had a major impact on the development of neuropsychopharmacology.

GS: In the 1970’s, a psychiatrist came to my office, closed the door and looked around in case anyone was listening, and then asked if I felt convinced that antidepressants worked.

TB: It took about eight years to show that they are effective. It was Klerman and Cole, about eight years after the introduction of imipramine who first conclusively demonstrated that.

GS: Yes and Karl Rickels wrote about the effects of non specific factors on treatment. It’s fascinating what expectation can do. This is where placebos
George M. Simpson

come in; to eliminate all the noise that comes with the improvement you get in the first week in inpatients and outpatients with depression. The problem is that many places around the world, as for example Japan, do not allow the use of placebo in studies on depression. I think that’s true in Europe now as well.

TB: In most of the studies with antidepressants there is about a 30 to 35% response to placebo against a 65 to 70% response to the active drug. That is a real concern.

GS: I think that is a huge concern. At the same time another reason for the problem might be in diagnostic practices, and I’m also a bit cynical about commercial testing. If I’m testing a drug and my living is dependent on the income, I put more patients into the study whether I’m doing it consciously or not. A study I didn’t mention yet, which I thought was one of the best we did, was a controlled inpatient study of 300 mg of imipramine vs. 150 mg. We had about 49 subjects and I think 47 out of 50 scale items showed greater improvement on the 300 mg. The WHO dose is still 150 mg as the upper limit. We had some psychotic depressions in that study. We obtained a 65% response rate for the non-psychotics and about 50% percent for the psychotics. So, I’ve always believed that many psychotic depressions take longer to treat and the idea they don’t respond to antidepressants may not be totally valid. If you read Slater’s biography, hospitals had many patients who were psychotically depressed and MDs had to tube feed them and we certainly don’t see this any longer.

TB: Didn’t you also study trimipramine?

GS: We looked at trimipramine because it was similar to methotrimeprazine. weren’t you first to report on trmipramine in the United States?

GS: Right. I looked at it at Rockland and it’s very similar to levopromazine and drugs used widely in the treatment of psychosis. So we looked at patients with schizophrenia but didn’t see any antipsychotic effect.

TB: You also did some research with MAOI and tricyclic combinations.

GS: Right. I still feel that a combination of a tricyclic and MAOI is safer than a MAOI alone. There’s a good pharmacological explanation for that based on animal studies and some human studies, including our own. Tom Cooper did some work in animals and when he gave them MAOIs and then tyramine, their blood pressure shut off. But if you pretreated them with tricyclics it didn’t. Probably, the combination was more efficacious in treatment but nobody ever studied it adequately. I used nortriptyline plus a monoamine oxidase inhihibitor. I would give nortriptyline at bedtime, because it appeared to help with sleep. It is one of those things that have remained controversial. If you’re talking about treatment resistant depression, that’s something you might want to do.
TB: Do you think that we made progress in the treatment of depression with antidepressants?
GS: We’ve made progress in safety. If my life depended on treating someone who was depressed, I would not use an SSRI. An advance would be that it’s more difficult to kill yourself with SSRI’s and that is significant. This reminds me of Jonathon Cole saying that a consultant psychopharmacologist went around and increased the dose of tricyclic antidepressants and decreased the dose of antipsychotics. The big advance would not be for psychiatrists so much but for non-psychiatrists; family practitioners used 75 mg of imipramine and because of side effects never titrated to a full therapeutic dose; now they can give SSRIs starting with a full dosage in the majority of people. It was a smart marketing ploy by Lilly to go after non-psychiatrists with these newer drugs. Only about 25% of psychotropics in the United States are prescribed by psychiatrists. At the same time the societal benefit would be that perhaps more people get treatment than before, because tricyclic antidepressants were more difficult to use. The studies comparing them are very few and the Danish cooperative study certainly showed that clomipramine was superior to fluoxetine and I would bet no shows the reverse. I also think nobody’s going to show fluoxetine less efficacious than other SSRI’s. That is something we should bear in mind.

TB: What about drugs like mirtazapine or trazodone?
GS: It’s difficult to prove anything more than that they have been shown different from placebo. I know very few psychiatrists who use trazodone, except maybe at bedtime for insomnia. I think mirtazapine and trazodone are effective drugs, but what their place might be still needs to be defined. Buproprion is used increasingly because it does not cause sexual dysfunction like the SSRI’s.

TB: What do you think about ECT?
GS: Most psychopharmacologists would say ECT is probably the most effective treatment for depression and it certainly got bad press that was partly deserved. The late Bob Kellner, who was a member of the ACNP, used to say of some colleagues that the only indication for ECT was the presence of a patient. That’s what gave it a bad press, but for severe suicidal, psychotic depression, catatonic symptoms it’s an excellent treatment. I was very happy to hear on public radio, Kay Jamieson talking to a very good interviewer who suggested psychotherapy for depression. She said unfortunately the kind of depression I have only responds to electrical treatment. The public is beginning to hear that and there are also articles talking about this. It’s wonderful that some well known people have
come forward and talked about their own depression, even some who have had ECT.

TB: So your first choice in depression is ECT?

GS: I would use it as a first choice in psychotic depression.

TB: We talked about your research with lithium earlier. Are you using lithium in treatment refractory depression?

GS: Yes. Lithium is a rarely used drug in our department because when valproate came they sold it to everybody saying it was the most efficacious treatment for bipolar patients, which is clearly untrue. It’s never been proven; the more serious studies suggest lithium is still the drug to beat and I would agree with that. I also think that the side effects of lithium are somewhat exaggerated. Some patients can be problematic, but we exaggerate it. I think there’s a good database to contradict the statement that lithium does not work for rapid cyclers or mixed states. It certainly helped the famous patient in England with 48 hours cycles. It’s hard to think of more rapid cycling than that. We should be careful to teach findings based on group statistics because individuals can behave differently. Regardless of the symptomatology, I still start any bipolar patients with lithium.

TB: What about carbamazepine?

GS: It’s all but disappeared from use and that’s probably because you need to monitor it like you need to monitor valproate and it also has sedative side effects. But most importantly it is not approved by the FDA for bipolar disorders and so it can not be advertised like valproate. We are getting all of these other anticonvulsants, some of which work and some of which do not.

TB: What is your first choice among the antidepressant drugs? Nortriptyline?

GS: Nortriptyline would be fine but it would depend on drug history.

TB: What would be your first choice drug in schizophrenia?

GS: All things being equal, I’d probably start with an atypical and the only reason would be to avoid EPS. There is evidence to support that. On the other hand, I think that low dose typical neuroleptics work quite well and while they do produce EPS, they can be minimized.

TB: Did you do any research with benzodiazepines?

GS: Not really. We did some pharmacokinetic work but never a lot. I have a fellow doing a benzodiazepine withdrawal study in patients with panic disorder. They are on an SSRI plus benzodiazepine, so we are trying to withdraw the benzodiazepines. I did a little bit in panic disorder but I worked mainly in schizophrenia and depression.

TB: Did you look at the effect of antidepressants in panic disorder?
GS: We started to look at nortriptyline in panic disorder when Ed Pi was in Philadelphia with the notion that if blood levels were useful in depression with nortriptyline, perhaps, it would be the same in panic disorder. We started a preliminary study, but Dr. Pi returned to California and we never completed it. Mostly the populations I had were inpatients with depression or schizophrenia and even the outpatients in the private sector when I worked in New York were predominantly depression.

TB: What about treatment of dementia?

GS: I've really never done research in dementia. We did a study with an antipsychotic in elderly schizophrenic patients but we were mainly concerned about blood levels and not with dementia.

TB: Let's try to review your activities chronologically. You did one year of residency, in Montreal then you moved to Rockland State.

GS: To Rockland, yes.

TB: You completed your residency there?

GS: Yes.

TB: How long were you at Rockland?

DS: Twenty years. I came to North America for a year and wanted to go back to London. I kept on postponing it but I never gave up the idea. It just sort of disappeared. I remember going to see Aubrey Lewis in New York but he told me they were only taking people who had boards in Internal Medicine before they went into Psychiatry. That didn't exactly encourage me to go back, so I stayed on, met my wife and that was that. It was comfortable at Rockland, since it was a big research environment. I mentioned Tom Cooper and Gene Laska who made my life easier. That part of my life was fun and it just sort of unfolded.

TB: Why did you decide to leave?

GS: I decided to leave Rockland and New York, because we needed an acute population to do clinical research. I thought we had set it up but it didn't work out. So I decided maybe it's time for me to change. I came out to California because Bruce Sloan was the Chair and there had been problems at a local state hospital that involved some sudden deaths, so the state funded a Clinical Psychopharmacology Laboratory unit. I came out to set that up. We did a couple of studies, but the medical director for the state got fired and the new person did not support a public hospital academic liaison. We wrote a couple of papers while I was there. One was on the Therapeutic Advantages of Research in which we described our findings with a group of patients we took off drugs for a week and nearly all of them improved. It brought up the fact that even patients with schizophrenia improve in a nice environment. That was done probably in 1978 and 1979 and published in 1980.
TB: It was also about that time you published on *Sudden Deaths in Schizophrenia*.

GS: That was a Task Force Report for the APA. There was a lot of talk in New York State in those years because of a series of sudden deaths in patients receiving haloperidol. So, the APA convened a task force, which I chaired. I suspect there have always been sudden deaths in people with schizophrenia, and nearly everybody was getting haloperidol in those years. It could be related to high dosages because studies in England showed that there’s a dose response effect on the EKG, related to QTc. Haloperidol at 10 mg is probably fine, but if you keep increasing the dosage to a 100 mg you get an effect. The APA report was inconclusive because there was no way at that time you could prove it unless you did a huge post-marketing study. I suspect the introduction of psychotropic drugs cut the death rate in hospitals substantially, but within the total population there might be one or two people who had a sudden death that was drug related.

TB: You moved from Rockland State to LA and from LA to Philadelphia.

GS: Wagner Bridger, after he took the Chair at MCP in Philadelphia had a goal of setting up a research team and invited me to come. When I asked, “to do what?,” he said, “Whatever you want.” I felt that was a nice offer so I went and we did quite a lot of interesting work, like the Treatment Strategy Study in Schizophrenia that showed again, that low dosages didn’t do badly. They had more threatened relapses, but we didn’t have more hospitalizations. It also showed that a psychoeducational program was as good as a very complicated behavioral intervention. We did some of our clozapine studies; a study in which we compared different doses of fluphenazine; and we looked at moclobamide in panic and depression.

TB: Where did you do the clozapine withdrawal study?

GS: It was done at Rockland. We withdrew it abruptly and had a lot of problems: nausea, delirium and a huge upsurge in abnormal movements. After that we did the study in people who had tardive dyskinesia; we showed that clozapine suppressed or at least improved it. We tried abrupt withdrawal again and again saw delirium, a huge upsurge of movements and nausea. Clozapine is probably the only antipsychotic drug I wouldn’t withdraw abruptly unless I absolutely had to in a case of white cell suppression. We even suggested that the withdrawal effects were cholinergic phenomena. Our conclusion of that 1978 study included most of what we know about clozapine; that it doesn’t produce EPS, it helps TD, can produce seizures, withdrawal effects and helps patients who did not respond to other antipsychotics.

TB: We started talking about the research you did in Philadelphia. Is there anything else you would like to add from that period?
GS: We did studies on smoking in schizophrenia. These were sort of epidemiological studies which showed a high rate of smoking in patients with schizophrenia. We did studies on water intoxication in schizophrenia with Jose de Leon and Cherin Verghese, and we looked at possible interventions, for example with clozapine. We did studies with a young German medical student who had developed a technique for measuring facial movements, so we looked at TD with his technique. And I did a lot of teaching and met a lot of fine people who I still keep in touch and work with.

TB: When did you move from LA to Philadelphia and when did you move back from Philadelphia to California?

GS: I came back to Philadelphia in 1984 and left again in 1994. We kept the house in the country in southern California and spent time there over holidays and eventually decided we would retire there. Some two months later I got a phone call asking me to take a teaching research position at USC. I still had an NIH grant running in Philadelphia, so I had to commute there and back for awhile. Then, I started to set up clinical research. There was no research in schizophrenia there. We have now a small research group in schizophrenia and research is going on in depression in adolescents and in PTSD in adolescents and adults. That’s been fun and interesting.

TB: You’ve had NIMH grants since the late 1950’s. Could you tell us something about the different grants you’ve had?

GS: After the ECDEU grant we had grants for our blood level studies and developing our scales for EPS and TD. We also had quite a bit of funding from pharmaceutical houses for all of these studies. When I went to California that was a state supported research unit which took a couple of years to get up and running but, as soon as it was up, the state had a change in leadership. So I went back to Philadelphia for nine years. Then, we had the Treatment Strategy study that was NIMH funded and the Clozapine Dose Response study, which went on for about six years. We also had grants for blood level study for fluphenazine. When I came back to California, and accepted the job offer my feeling was that I would work for a year or two setting things up and then disappear onto the golf course, but I kept on. We hadn’t put in any NIMH grants because of my concern that I needed somebody, who would not only do the work, but be there to complete it. So, we’re getting close to that stage now.

TB: You have interacted with the pharmaceutical industry for several decades?

GS: It was much more casual and intimate in the early years but over time it evolved, like industry itself. It’s become more and more difficult; it’s hard to keep up with people. The industry has many people and they all
seem to move around a lot but now it’s much bigger and everything is more complicated. There are multi-center studies but they do not allow any piggyback study that might interfere with the main study. Companies have become much more focused because the FDA has been more scrutinizing. So if you ask what I think about it, I can’t say I’m happy. Do I know how it could have evolved differently? I’m not too sure because the pharmaceutical company is there to make money and that was probably always true. Of course there is this influence in the whole of medicine; the marketing techniques are questionable for some. That seems to be escalating.

TB: You have been at least on one NIMH committee I know of.
GS: I was on the Treatment Assessment Group at NIMH and I chaired it for a couple of years. It was a good education. Mike Goldstein was on that committee and he was a very superior, objective person, so I learned a lot from him. He knew what was happening in the field. Then I did site visits and those sorts of things, which were time consuming but interesting.

TB: Is there anyone who had a major impact on your professional development?
GS: A few people in Montreal like Bruce Sloane and my encounters with Heinz Lehmann. I think you are aware that he made one of his typical statements that nobody who only spoke English could ever understand existentialism, so I stopped trying and that saved me a lot of time. Then he taught me a most helpful thing the need to change models in treating patients in different phases of their illness; he was really an excellent clinician and teacher. At Rockland I never saw Nate teach but I heard him give lectures. Eventually, I’d say I learned from nearly everyone in the ECDEU because they were friends; although we did much the same things each of us had hown area of interest. That was a very useful group. Gene Laska and Hillary Lee, who worked with me, both knew far more about statistics, data management and handling and taught me in that area. They were not formal mentors but I learned from people who were around me or just by seeing patients.

TB: Would you like to mention any of the people you collaborated with?
GS: Philip May; we met through the ACNP, became friendly and then worked on chapters for Freedman and Kaplan.

TB: What were the chapters on?
GS: The treatment of schizophrenia. It was nice to work with somebody who was stimulating and I learned from him many things. I collaborated with Bob Kellner, because he was somebody I met in the anatomy department at Liverpool who became a very close friend. I guess he, Philip May and Don Gallant were the closest friends I had in this country. I used to meet Bob Kellner at the ACNP and maybe one other meeting and we
occasionally visited, but if he’d hear a good joke he would always phone me. We used his depression scale in our imipramine study. I worked with Don Gallant in a Depression Symposium in New Orleans. Then, I worked a bit with Jonas Dencker in Goteborg.

TB: Would you like to mention by name a few people who worked with you or trained?

GS: I had Scott Angus working with me and then he went to Canada and still lives there. Poddy Harper and Mark Branchey worked with me. Then, Guy Edwards came for a couple of years. I collaborated and worked with Doug Levinson and Ira Katz, who are now at Penn. Alan Bellack was a bright psychologist and he worked with me on the Treatment Strategies study; he’s now in Baltimore. Jose de Leon worked with me for a couple of years as a Fellow, published quite a bit and still goes on publishing. He’s now in Kentucky.

TB: You are a member of many organizations. Weren’t you the first president of the American Society of Clinical Neuropsychopharmacology?

GS: No, I was one of the small groups of people who were concerned about clinical psychopharmacology. The idea was to have an organization that would help to get information about clinical psychopharmacology to practitioners. Gerry Klerman and Don Klein called a meeting in Washington where this organization was born. I see this as an educational arm to the science organization. The new organization had something like 100 members, and I don’t know whether it has had an impact on clinical practice or not, but that was the intent there.

TB: When did you become a member of the ACNP?

GS: In the mid 1960’s. It was Nate Kline who suggested I should apply for membership. It was easy to become a member relative to today. I became a member and the meetings were unique, because you got a chance to meet nearly everybody. At a meeting like the APA, you have to search out people and if you want to talk to them, you probably have to have lunch or dinner. At the ACNP, you could have a half an hour by the pool. So, you got to see and meet a lot of people in the field who were doing different things.

TB: You were president of the ACNP?

GS: Yes, in 1991. I served on the Council for three years, then I was president elect and finally I was president. It was a good experience. There are some things that the ACNP is engaged in that are unique and novel but others I don’t know how productive they are.

TB: Like what?

GS: Like going to Washington and up on the hill to bring to the floor the sort of needs in science and our own field. You know as well as I do, it’s a very unique organization.
TB: Would you like to mention any other organizations you are a member of?
GS: The APA, the Society of Biological psychiatry and the Royal College of Psychiatrists.
TB: Are you still working full time?
GS: Yes, I am.
TB: What would you consider your most important contribution in the field? You created the Simpson-Angus Extrapyramidal Symptom Rating Scale.
GS: That was useful for us at that time. You have people who have blinding insights and make advances and you also need a group who do the tidying up work, which is important. I think I helped advance clinical practice by doing some of those small things. The imipramine study was important because it was one of the first that made any comment about the effectiveness of tricyclic antidepressants in psychotic depression although that question is still open. It showed that you may need higher dosage. All of our works on side effects, withdrawal effects were important.
TB: You were also the first author of the TD scale.
GS: That developed in the midst of controversy about TD. First we had an overinclusive scale, but then shortened it. We had the intention of examining postmortem the basal ganglia of patients who had TD vs. patients who did not, but that did not work out.
TB: You are a recipient of several awards. Would you like to mention some of the distinctions you received?
GS: In Philadelphia I got the Alfred Noyes award for a body of work in schizophrenia. I got the Heinz Lehmann award and that pleased me a lot, since he had been a teacher and mentor. I got an honorary degree from the University of Goteborg for work that made a contribution to the field and had collaborated with people at that university. That was good; I had dinner with Jonas Dencker, Arvid Carlsson and Gottfries all distinguished people, Arvid being the most distinguished.
TB: How many papers did you publish?
GS: Probably 300.
TB: Would you like to say something about one or another?
GS: I like what I wrote on Neuroleptic Malignant Syndrome. It’s a practical guide to how to avoid and how to treat it.
TB: What about books?
GS: I’ve written a lot of chapters in books, but the others were more like booklets. I was on the original task force on Tardive Dyskinesia, so our report was a monograph, and another short monograph was on Sudden Death. That’s about what I’ve done. Even writing book chapters I’ve tried to avoid.
TB: You’ve witnessed forty years of psychopharmacology. What are your thoughts about the changes?

GS: Mostly I feel positive. We have proven drug treatments, even though they may not be as efficacious as we would like, that’s a huge change. When I went to Rockland in 1958 and worked at a local mental health clinic I had a man with panic disorder who, occasionally when it happened, would get out of his cab and wouldn’t cross the George Washington Bridge. I was told by my supervisor he was suffering from homosexual panic. I talked to a friend in England and asked if I should give him a monoamine oxidase inhibitor. He said, sure, and I did that and the homosexual panic went away. It was also dramatic to see some of the depressed patients free from their symptoms. No matter what anyone says, these are dramatic changes. In schizophrenia there were no drug treatments until the antipsychotics came along. Progress in the treatment of schizophrenia has been disappointing because we have not made any giant leap forward after chlorpromazine. Then in mania, in severe bipolar illness I used to give prophylactic or maintenance ECT, but after lithium came along I did not need to do this very often.

TB: Are you pleased with the direction the field is moving?

GS: I cannot be displeased. The whole neuroscience component is a big plus. Imaging and genetics are exciting for psychiatry. There is no payoff as yet, but there will be. It’s easy to focus on these new methods and underestimate the value of clinical contributions. To do a good clinical job takes a long time and it’s not certain that you will be rewarded. But if you don’t spend the time, all the high science in the world just creates confusion.

TB: What would you like to see happen in the future in psychiatry and psychopharmacology?

GS: I would like to see the genetic links to all the major illnesses. I think we are some way from that, but the technology seems to be there. I can see where nosology might get in our way because we can see in schizophrenia a group of illnesses; it creates problems if we treat them as one entity and lump them together in imaging or genetic studies. Yet, there is no easy way to separate schizophrenia into clinical groups. I don’t know whether biological markers might mean we can attack the problem from the other way around. I would like to see more potent and rapidly working antidepressants and, in terms of anxiety, we could probably get a better drug although I think we do reasonably well there.

TB: On this note we should conclude this interview with George Simpson. Thank you, George for sharing this information with us.

GS: Thank you.
RB: Today is December 12, 2007. We are in Boca Raton, Florida. My name is Robert Belmaker and I am interviewing Professor Herman M. van Praag about his career in psychopharmacology. Could you tell us about your early education and how you became interested in psychopharmacology?

HvP: I was born and went to school in the Netherlands. My father’s family lived in Amsterdam since the late sixteenth hundreds, when they were expelled from Prague, the town they lived in, by one of the kings of Bohemia. Praag is the Dutch name for that city. From mid-1942 to the end of the Second World War I was incarcerated in German concentration camps. After the war I continued secondary school and then decided to go into medicine. I was also considering biology or political science but from the very beginning I had a great interest in brain and behavior, body and soul. I still think the way the brain enables us to do what we can do, to behave the way we like to behave, to feel what we experience is the most fascinating problem, enigma rather, men is confronted with. After I completed medical school, I started training in neurology but in Holland, that time to become a neurologist, you had to spend one and a half year in psychiatry. By chance I started my training in psychiatry. Those were the years when the neuroleptics, antidepressants and lithium were introduced and all of a sudden it appeared to me it should now be possible to study the relationship between brain and behavior experimentally. The body-soul relationship was not an exclusively philosophical problem anymore. I became interested in what those drugs were doing in the brain, and if there was anything wrong in the brains of people who responded to them. So that brought me into psychiatry, instead of neurology.

RB: Very interesting! Could you say a bit about the first years of your career and your first research project in psychopharmacology?

HvP: First I had to go into the Army for two years and since I had, as a student, already done some research in neurology – studying mental and bodily consequences of brain injury – I was asked whether I would be interested to do more. So a large part of the two-years were spent in the laboratory studying all kinds of mycotic infections in military personal, at the time a medical problem in the military. Then, the day after I left the Army, I began training in psychiatry. It was 1958 and the antidepressant effect of iproniazid, the first monoamine oxidase inhibitor (MAOI), had just been discovered. It was the first of the new psychotropic drugs of which something was known about its action in the brain. I treated a few
patients with iproniazid and was amazed that several of them improved tremendously within a few weeks. So I decided to try to study what MAOIs did in the brain of humans and whether there was any evidence their effect on monoamine oxidase had any relationship to their therapeutic effect. It took some time before the head of the laboratory at the hospital, a biochemist, named Leynse, decided to let me start; in those years psychiatrists were not particularly known for their scientific acumen, but then we worked together for a number of years. That was my first project and the very substance of my thesis on monoamine oxidase inhibition as a therapeutic principle in the treatment of depression. I finished my residency in 1963, defended my thesis in 1962 and became a psychiatrist, in the Department of Psychiatry of the University Hospital of the Erasmus University in Rotterdam. Shortly after, I got a phone call from a former general practitioner who was a member of the Board of Directors at the University of Groningen. He had read my thesis, found it interesting, and asked whether I would be interested in setting up a department of biological psychiatry at his University. I said yes and made plans for a clinical unit with four basic science laboratories: pharmacology, biochemistry, electrophysiology and animal behavior studies, in the Department of Psychiatry. The university approved the plan and the department opened in 1966. It was the first department of this kind in Europe.

RB: Do you know anything more about what might have been the reason for the university’s interest

HvP: It was the physician who read my thesis and, for one reason or another, felt biological psychiatry was a fascinating new field, a novum that should be introduced at the University.

RB: Was there anything in the psychiatric literature at the time that you think had influenced on your early ideas and desire to enter this new field?

HvP: I don’t think so. In Holland, I had no mentors in that field, because there was nobody involved in biological psychiatry and even in Europe there were only a few people. Of course in America there were more people involved already in the 1950s.

RB: So you had probably read some publications by Seymour Kety and Joel Elkes. Did you meet them?

HvP: No. I met them only afterwards at conferences in the 1960’s, particularly at the ACNP.

RB: Could you say a few words perhaps about the conferences you found most productive in terms of your interest?

HvP: No doubt that there were the meetings of the Group for the Study of Affective Disorders. This was a group of about 15 people and we met
every year for discussions and interaction that were an enormous stim-
ulation. Members were, amongst others: Ole Rafaelsen, Alec Coppen,
Mogens Schou, Michael Shepherd, Kaj Gottfries, Fred Goodwin and sev-
eral others. It was a small working group but very active. There were new
discoveries almost every month so it was a very exciting time.

RB: Could you say something about those discoveries?
HV: Serotonin (5-HT) was discovered, first in the gut and then, later in the
1950’s, in the brain. It was recognized as a neurotransmitter and shown to
interact with LSD (lysergic acid diethylamide). In the late 1950’s dopamine
(DA) was also shown to be a neurotransmitter in its own right. New hori-
zons opened up, but there was no one in Holland to teach me about
these discoveries and not many people in Europe because the field was
just starting. I had to teach myself.

RB: Could you say something about your most important findings in the first
third of your career?

HV: In the first ten to fifteen years our research was focused mostly on sero-
tonin. Interest was split in those years between people interested in
noradrenalin (NA) and serotonin (5-HT). More people were interested in
NA because of the NA hypothesis of depression, but, after a couple of
years of research, we could demonstrate that there were disturbances
in 5-HT metabolism in depression. It was a fascinating finding that there
were disturbances in a particular transmitter system, in specific types
of depression. We also recognized that research in biological psychia-
try must be based on precise diagnoses and precise measurements of
behavior. Without that the whole business of biological psychiatry would
make no sense. It seemed highly unlikely that vaguely characterized
diagnostic constructs are underpinned by well-defined neurobiological
deviations. Diagnosis at the time was all over the place. Almost every
textbook writer had his own classification; psychometric methods were
not available.

We developed for depression a standardized, multiaxial diagnostic
approach, long before the DSM III was introduced. Furthermore, we tried
with a group of psychologists to standardize the diagnostic instrument of
psychiatrists: the interview. This resulted in the Vital Syndrome Interview;
the first standardized, structured interview in psychiatry.

Later we moved away from nosology. Why? I saw too few patients
that met the diagnostic criteria of a particular nosological entity. Inter-
osological borders seemed extremely fuzzy. At that point, in the early
‘70s, we resorted to an approach I called functionalization of psychiatric
diagnosis.

RB: What do you mean?
HvP: It means, dissecting syndromes into parts: the psychopathological symptoms and the psychic dysfunctions underlying the psychopathological symptoms. Psychopathological symptoms are the way those psychic dysfunctions make themselves known to the patient and the observer.

We began to search for the biological underpinnings of psychic dysfunctions, generating psychopathological symptoms, rather than the cause of a particular depression-type.

RB: When did you publish on this?
HvP: From the early 1980’s on.

RB: Do you see your functionalization of psychiatric diagnosis as a forerunner to your book on denosologizing psychiatric diagnosis and of current criticisms of the DSM system? Do you think that your book planted the seeds and influenced that debate?

HvP: I hope so and think so. My name is not always mentioned, but it doesn’t matter, I am not overtly narcissistic. If we continue to use DSM diagnostic entities we will never progress in biological psychiatry. It would be an absolute miracle to find the cause of schizophrenia or major depression. The idea you can correlate psychic dysfunctions with biological dysfunctions has opened up the possibility developing a truly scientific basis for psychiatry.

RB: Could you say something about your first team in Groningen?
HvP: It was, from the beginning, an interdisciplinary group. We had in the department psychiatrists, psychologists, biochemists, biologists, physiologists, and we closely worked together with experimental neurology, pediatrics and the Department of Biology, that had a strong interest in ethology. With pediatrics we ran a program on inborn errors of metabolism leading to behavioral disorders.

RB: Could you say something about your sources of funding and support?
HvP: That was mainly from State agencies. We got money for pure and applied research and there was a third stream from the university itself. There was almost nothing from industry because until the 1980’s we were encouraged not to accept money from them. That has now changed completely. Universities were paranoid about money from the industry. I have always said, if it is open and transparent in the form of a contract, there is nothing against it; but the university was not convinced.

RB: Could you say something about your move from Groningen to Utrecht?
HvP: I was invited to Utrecht to chair the department of psychiatry as a whole. In Groningen it was a new chair of biological psychiatry. In Utrecht it was the general chair of my former teacher Rümke. It was in the mid 1970’s and in Holland psychology and psychoanalysis still dominated psychiatry. It was also the time of the anti-psychiatry movement with completely
exaggerated ideas about social determinants of abnormal human behavior. I felt accepting the general chair of psychiatry would give me an opportunity to explain the professionals in psychiatry as a kind of missionary about the new biological approach. When I arrived to Utrecht there was very little research in the department. We continued our research on monoamines and depression, aggression, anxiety and impulse control. We also became interested in peptides, endorphins and collaborated in that with the Rudolf Magnus Institute of Pharmacology, headed by David de Wied. Then, five years later, I was invited to the Albert Einstein College of Medicine in New York.

RB: Where did you develop your technique for spinal fluid research?
HvP: In Groningen.
RB: And you continued with that technique in Utrecht? You used that technique extensively.
HvP: Yes, for quite a number of years because we found baseline values of 5-HT metabolites in CSF informative to a certain degree, but not enough. Next we developed the so-called probenecid technique providing information on serotonin turnovers in the brain. That was we felt a step forward.
RB: Then, you moved to Einstein. What year was it?
HvP: In late 1981.
RP: What were your reasons for moving?
HvP: That is a complicated and interesting story. I went to Einstein to become chairman of psychiatry at a famous medical school. They also asked me to boost research and to merge the Einstein Department with the Montefiore Hospital Department and their affiliated institutions, twelve in total. I like research and I like management. Although the managerial job I had, I carried out with tremendous enthusiasm, even passion, it was attractive to go to another country. I also found the invitation an honour that I could not deny. Last but not least the invitation concerned the only Jewish University outside of Israel. That brings me to another point; in 1976 or 1977 I was visiting professor in Israel, at the Dep of Psychiatry, Hadassah Hospital, Hebrew University Jerusalem.
RB: Perhaps you could say something about your several sabbaticals and collaborations in Israel and how that fit in with your career. You have been influential in the development of psychopharmacology in Israel.
HvP: It was not a sabbatical; I was asked to become the chairman and head of the department of psychiatry.
RB: That was in?
HvP: In 1976. My spiritual background is Jewish. Judaism is dear to me. Zion is dear to me. My grandparents from both sides belonged to the first Zionists group in Holland. My parents were Zionists. I was raised in a very
Zionist milieu. When I came back from the concentration camps my sister went to Israel but I said to her, I first want to finish my studies and then follow you. Meanwhile, in 1948, Israel was established. I finished medical school and said I will specialize first and do my thesis, so I still didn’t go. Next I got the invitation to establish a Department of Biological Psychiatry in Groningen. So, I postponed aliyah again. Then, finally, I got the invitation to become Chairman of Psychiatry at Hadassah and felt that was an enormous opportunity, so I went, to begin with as a visiting professor, because I wanted to gauge whether I could do the job.

RB: The invitation from Hadassah was based on your scientific work.

HvP: Yes. I went alone, which was probably not a good idea. My wife stayed in Holland because of our oldest son was sitting for his matriculation. Well, you know the end of the story; I didn’t stay. It was mainly because of the language. If I couldn’t answer the telephone, read the reports and speak with patients, how could I function? So, I went back. It was a very difficult and painful decision. A few years later I got the phone call from Einstein. I said, this is not the true Jerusalem, but for me it is at least little Jerusalem. So, that has been the case. But believe me, I have worked with great enthusiasm in Jerusalem and all through the years until this very day, the question has been was it the right decision to leave? Who knows?

RB: I think only great men have regrets. You talked very passionately about your concepts about monoamines, psychopathology, functionalisation, vital depression. The latter term your name is associated with. Are you still for the diagnosis of vital depression and is vital depression something like melancholic depression in the DSM-IV?

HvP: I have not left the idea of vital depression behind. It is related to the syndrome described in the DSM under the heading melancholia. However, in the DSM-IV the term melancholia is used for a kind of severe depression whereas vital depression can be of different severities. As said, symptomatologically vital depression is close to melancholic depression. More generally speaking, I think syndromal differentiation is important, and to move from syndrome to symptom differentiation, and from there to analysis and measurement of underlying psychic dysfunctions.

RB: You have been involved in teaching and training people for many years? Could you say something about that?

HvP: Already as a resident I had teaching responsibilities. Since 1963, after finishing residency, I had many residents and research fellows, and I hope I have had an impact through them on the development of the field. I am something of a missionary. I like to preach and convince people about my ideas. But if they don’t agree, I can stand that. I am no scientific bully.
RB: In Israel there are many who consider themselves your students. But it is true, as we all know, that our students don’t necessarily agree with everything that we say. I believe you were at Einstein for a decade?

HvP: For eleven years.

RB: Were there any particular scientific activities you emphasized or promoted there?

HvP: I promoted research in general, not only biological research. The biological program grew rapidly. I established a number of labs; neurochemistry, neuroendocrinology, genetics and animal behavior. We continued our research in the regulation of anxiety, mood and aggression on a larger scale than in Holland. There were many more people in the department, and there was more money available. We had a close collaboration with neurology and that was very productive. Apart from the programs I was personally interested in, there were several others, e.g., in the biology of sexual behavior. We had a number of excellent people at that time. Previously Einstein had been, of course, the Mecca of psychoanalysis, together with the New York Psychoanalytic Institute.

RB: Dedicated mainly to psychoanalysis?

HvP: Yes. When I came, I think they thought I was a true barbaric, an uncivilized biological psychiatrist. They were afraid I would be firing everyone. I didn’t. What I didn’t like was the one-sidedness. Hundreds of psychologists and psychiatrists, almost all of them analytically oriented. One and a half behaviorist! I found that unacceptable. I have built up a department clinically speaking multi-dimensional and with a strong research orientation, biological and otherwise. Of course psychoanalysis was not thrown out, but it became one orientation among others.

Moreover I found my managerial duties fascinating. It brought me in close contact with city and state officials, with the New York political machinery. I found that interesting and captivating. That isn’t how it is in Holland. As a Chair, you do not negotiate with political authorities; that is done by the Board of Directors of the hospital.

RB: Are there many awards and honors that you have received in your life? Is there any that you are particularly proud of?

HvP: Well, I have my share, and I like them all very much. I found my knighthood very special. I was knighted by the queen of The Netherlands, because of my scientific contributions. My election to membership in the Royal Society of Sciences of the Netherlands is also special. There were only twenty elected members from medicine and no psychiatrist in the Royal Society.

RB: So you were the first psychiatrist in history elected as a member of the Royal Society?
HvP: Yes, and that is what I liked very much! My foreign awards and distinctions I value very much too.

RB: Could you say something about Maastricht?
HvP: I left New York for Maastricht, though I loved the city and my job. We left to be closer to our 4 children and 12 grandchildren.

I was invited to be the Chair of Psychiatry at Maastricht University to boost research and to unify three more or less independent departments of psychiatry that existed in that medical school! It was a job that I carried out with great pleasure. I am now an emeritus professor but still scientific advisor to the Department.

RB: In the last minutes you might like to say something about your current work as Chairman of the World Psychiatric Association’s (WPA’s) Section on Psychiatry and Religion. Do you see this as a continuation of your career in psychopharmacology and biological psychiatry or is this a hobby you developed in your retirement?
HvP: It used to be a kind of hobby for a great many years, and one that is a great interest to me and close to my heart. I have published about it quite a bit, but few people in the psychiatric field knew, because I was too much identified with biology. Religion and religiosity are nowadays neglected or ignored in psychiatry, as biology was in the 1950s when I started my career. Interestingly there is now an upcoming field of neurotheology that studies brain circuitry possibly related to spiritual and religious sensitivity. It is connection between religiosity and biology that opens up fascinating research opportunities.

RB: One last and possibly delicate question. Did the camp experiences in the early 1940s influence your professional career?
HvP: No they did not. I only want to say this about that period. I came out stronger than I went in. Pre-camp I was a somewhat timid and insecure boy; when the nightmare ended, I had grown into an assertive, if not potentially aggressive man.

Damaged survivors have gotten much attention, rightly. Those who maintained their strength or augmented it got much less. Thank God, I belonged to the latter category. I have lived a life in which productivity and happiness returned.

RB: Thank you very much, Professor Herman van Praag.
HvP: And, I thank you, Doctor Belmaker.
INDEX

Note: The page numbers for each interviewee’s entry appear in boldface type.

Abikoff, Howard, 230
Abrams, Richard, 12, 82, 94, 96, 98, 100
Abramson, Harold A., 140, 239
Addiction/dependence. See Drug abuse/ addiction
Adverse effects. See Side effects
Agranulocytosis, 4, 9, 11, 53
Akathisia, 3, 299
Alexander, Franz, 113
Alexander, George, 277
Alles, Gordon, 143
Altschuler, Mark, 137
Alzheimer’s disease, xv, 26, 129, 132, 168, 178, 181, 186, 188
American College of Neuropsychopharmacology (ACNP), xxxvii, xxxviii, xlv, 34, 96, 151, 177, 193, 195, 249, 263–64, 265, 266, 267, 283, 298, 304, 309, 310, 314
collaboration with NIMH, 253–53 and ECT, 95, 102
establishment, xxxix, 16–17, 150
neuroscience/basic science emphasis, 18, 103, 196
pharmaceutical industry ties, 103–4
American Psychiatric Associaton (APA), xlv, 23, 65, 128, 197, 214, 310
pharmaceutical industry ties, 103–4, 159
task forces, 27, 97, 98–99, 307
American Society of Clinical Psychopharmacology (ASCP), 103, 310
Amitriptyline, xviii, 13, 15–16, 25, 29, 148, 165, 175, 176, 302
Amobarbital, 26, 60, 75, 84, 93
Amphetamine(s), 5, 21, 26, 143, 239–40, 254
as antidepressants, xxii, 166
psychosis, 66, 183
Andreasen, Nancy, 124
Angrist, Burt
as interviewer, 183–91
Angst, Jules, 202
Angus, Scott, xx, xxviii, 291, 310
Antianxiety agents, xix, 9, 47, 51, 54, 55, 175, 209, 248, 250, 272. See also Tranquilizers
vs. antipsychotics, 49, 262
Anticonvulsants, 45–46, 110–11, 114, 291
as mood stabilizers, 103, 305
See also Monoamine oxidase inhibitors (MAOI); Selective serotonin reuptake inhibitors (SSRI); Tricyclic antidepressants
corphromazine as, 81, 209
EEG screening, 175, 178
vs. antipsychotics, 148
Anti-Parkinsonian agents, 8, 81, 209
Antipsychotic agents, xix, xx, 4–9, 32, 81, 146, 147, 151, 166–67, 206, 215, 223, 248, 253, 260, 280–81, 291, 294, 295, 303, 307, 312. See also Neuroleptics
atypical, 103, 160, 161, 210, 258, 262, 263, 297–99, 304
EEG screening, 175, 178
in psychotic depression, 81–82, 148
Byerley, William, 186

Cade, John, 160

Cahn, Charles, 25

Cameron, D. Ewen, 23–24, 281, 285, 286–87

Cannon, Walter B., 219

Carbon dioxide (CO₂), xxii, 26, 65, 211, 216–18, 229

Carlsson, Arvid, 160, 170, 270, 311

Carpenter, William T., Jr., 184, 258, 264

as interviewer, 243–55

Carroll, Bernard, 83

Carter Products/Carter-Wallace, 45, 47–48, 50–52, 54

Castellanos, Gaston, 28

Castellanos, Xavier, 211

Castillo, Aitor, 28

Catatonia, xv, xix, xxvii, 77, 82, 93–95, 100, 101, 178

periodic, 288

Catecholamine(s), 25, 184, 216, 286

Cattell, Raymond, 50

Caulfield, Patricia A., 270

Ceskova, Eva, 28

Chein, Isidore, 238

Child psychiatry, 58, 108, 183, 230

psychoanalysis, 110–11

Chlordiazepoxide (Librium), xviii, 10, 51–52, 69, 118, 152–53, 244, 272–74

Chlorpromazine, xviii, xxi, 3–4, 6–7, 8–9, 11, 24, 26, 49, 93, 100, 112, 162, 294, 297, 300

EEG effects, xvii, 83–89, 172, 175


studies, 63, 67–68, 70, 81, 145–17, 224, 239

Cholinergic system/hypotheses, xxii, 100, 168, 185–190

CIBA (pharmaceutical company), 3, 136–39

Classification, psychiatric, xiii, xiv–xvi, xix, xx, 34, 117, 196–97, 198, 200, 231, 318

consensus-based, xii, 31

Leonhard, xlv, 30–31, 300

Cleghorn, Robert, 287, 287

Clinical trials/studies, xxi, xl, xxxix–xlii, xliii, xlv, 28, 32, 47, 194, 203, 213, 250, 289, 293

methodology/guidelines, 196, 251, 253, 255

phase II studies, xlv, 207

Clozapine, xx, xxi, 92, 163, 260, 261, 262, 292, 294, 296, 297, 299, 300–1, 307, 308

Clyde, Dean, 65, 67

Cohen, Mandel, 217


Collegium Internationale Neuro-Psychopharmacologicum (CINP), 16, 22, 150–51, 170, 177, 221, 252, 264, 267, 290

history series, 34, 54, 274

Rome meeting (1958), 4, 85, 172


Congress (U.S.), 50

psychopharmacology funding, xxxviii, 10, 63, 65, 82, 194, 246, 254


Controlled studies/trials, xxxix, xlii–xliii, 6–7, 151–52, 210, 211, 217, 238, 248–49, 303

Cook, Leonard, 6

Cooper, Thomas, xx, 295, 303, 306

Coppen, Alec, 315

Cortisol, 59, 102, 216–17, 258

Costa, Erminio (Mimo), xli, 246

Cosmides, George, 246
Cranswick, Edward, 288
Cravey, Robert H., 126
Crick, Francis, x
Cullen, William, xiv

Dattner, Bernhard, 75, 77
Davidoff, Leo, 74
Davis, John M., xx, 66, 159, 184–85, 187, 286, 299
as interviewer, xxxviii, 205–30
Davis, Kenneth, 168
Delay, Jean, xxxix, 278
De Leon, Jose, 308, 310
Dementia, xiii, xv, 32, 178, 306. See also Alzheimer’s disease
vascular, 26, 142
Dementia praecox, xiv, 222. See also Schizophrenia
Denber, Herman (Hy), 80, 86, 251, 280, 290
Dencker, Jonas, 310, 311
Deniker, Pierre-Georges, xxxix, 69, 164, 166, 278–80
Depression, xix, xv, xx, xxi, 15, 26, 68, 183–85, 196–99, 224, 286, 310, 317
adolescent, 231, 308
and anxiety, 16, 166, 201
atypical, xxxviii, xlii, 210–11, 214–15, 223
causation hypotheses, xxii, xlii, 180–81, 315
major, 31, 316
psychotic, 70, 81, 148, 257, 277, 303, 304–5, 311
reserpine and, 138
treatment, xxii, xlv, 11–12, 20, 55, 57, 64, 103, 148, 225, 260, 270, 271–72, 274, 287, 302–6, 312, 314
vital, xx, xlv, 31, 318

Desjardins, Raoul, 90
Desipramine, xiv, xx, 25, 165, 202, 287, 289, 301
Detre, Thomas, 257

Deutsch, Anna, 107
Deutsch, Felix, 107, 109
DeVerteuille, Roger, 25
De Wied, David, 317
Dextroamphetamine, 21, 60, 143, 155
Diagnosis, psychiatric, 104, 112, 196, 199, 200, 210, 214, 223, 231, 281, 315–16
and drug response, x, xx, 29
heterogeneity, xii, xix, 30–32, 100
Diazepam (Valium), 10, 52, 118, 153, 244, 272
Dinovo, Eugene C., 120, 126
Dix, Dorothea Lynn, 277
Dixon, Lisa, 253
Dopamine, xi, xxi, 9, 147, 165, 168, 184, 188–89, 270, 271, 315
hypothesis of schizophrenia, 8, 154, 160, 185
receptor blockers, 162, 263, 291, 300
serotonin interaction, 260, 297
Dornbush, Rhea, 100
Double-blind studies, xli, 137, 144, 147, 193, 207, 209, 296, 297
Drug abuse/addiction, 10, 61, 70, 77, 176, 234–35, 242, 247 See also US Public Health Service (USPHS) Hospital, Lexington, KY
juvenile, 238–39
potential, 52, 206, 236
DSM series/system, xl–xliii, xlv, xlvii, 102, 104, 197, 200, 203, 213, 230, 316
DSM-II (1968), 66, 164, 214, 225
DSM-III (1980), 213–14, 224, 229, 281–82, 315
DSM-III-R (1987), 31, 229
DSM-IV (1994), xii, 35, 117, 281
DSM-5 (forthcoming), 95, 101, 104, 229
Durrell, Jack, 183, 257, 258, 261

Early Clinical Drug Evaluation Unit (ECDEU)

network/program, xliii, xlv, 24, 68–69, 85, 152, 177, 249–51, 288, 290, 292, 295, 308, 309
assessments manual, 25, 251
Eddy, Nathan, 156, 236

Efficacy, therapeutic, xi, xix, xxi, 29, 63, 166, 251, 252, 292, 298–99, 304
commercial/regulatory aspects, xli, xlii, xlv, 64, 248–49
dosage issues, xx, 92
Efron, Daniel, 249, 250
in catatonia, 93–95, 101, 304
EEG effects, 84–86
in psychotic depression, 82, 277, 304–5 regressive, 23
in treatment studies, 6, 7, 80–81, 83–89, 91–92, 95, 152. See also Quantitative EEG
Elkashef, Ahmed, 253
Elkes, Joel, 138, 245, 246, 314
Ellis, Albert, 301
Endicott, Jean, 200
Engel, George, 112
Epilepsy, 17, 20–21, 53, 110
and EEG, 83, 174
psychological aspects, 111
Epidemiological studies, xi, 31, 201
pharmacoepidemiology, 250
Evarts, Edward, 62
Simpson–Angus rating scale, 311
Falret, Jean-Pierre, xiv
Fann, Ed, 184
Felix, Robert, 110
Ferrero, François, 28
Feuchtersleben, Ernst, xii
Fillp, Vaclav, 28
Fink, Max, xvii, xix, xliii, xlv, xlvi, 12, 73–104, 172–73, 175, 178, 179, 180, 207, 208, 221, 223
Fish, Frank, 30–31, 286, 300
Fisher, Seymour, 65, 298
Flügel, Fritz, 172, 175
Fluoxetine (Prozac), xix, 91, 92, 167, 304
Fluphenazine, 5–6, 8, 65, 67, 252, 293, 298, 307, 308
Food and Drug Administration (FDA), xli–xlii, xlvii, 10, 26, 52, 64, 292
drug approvals, 6, 44, 46, 47, 48, 91, 161, 206–8, 251, 273, 305, 309
efficacy requirements, 64, 207
Forrest, Irene, 294
Frazier, Frank, 242
Freedman, Daniel X., 155, 240, 257–58, 261, 262, 263
Freeman, Harry, 240
Freud, Anna, 286
Freud, Sigmund, 19, 58, 61, 109, 171, 205, 215
Freyhan, Fritz, 4, 15, 33, 145, 245 ...
Fricchione, Gregory, 94
Friedhoff, Arnold, 98, 153–54
Friedman, E. D., 74, 77
Fromm-Reichmann, Frieda, 286
Fuller, Raymond, 261
Gabbay, Vilma, 231
Gallant, Donald, 68, 69, 251, 290, 296, 297, 309, 310
Gantt, Horsley, 22
Garbutt, James C., 189
Gardos, George, xix
Garrod, Archibald, x
Gaszner, Peter, 31
Genetics, xi–xii, 255, 258, 260, 266–67, 268, 312
Gerard, Donald, 238
Gerard, Ralph, 49, 62, 139, 195
Gershon, Samuel, 154, 160
Giarman, Nicholas, 257
Gildea, Edwin, 107
Gillin, J. Christian, 133, 186
Glaser, Gilbert, 76
Glassman, Alexander (Sandy), 82, 165
GloD, Carol, xix
Gold, Harry, 58, 144
Goldberg, Solomon, 65, 66, 250
Goldman, Douglas, 15, 112
Goodman, Louis, 195
Goodwin, Frederick, 184, 216, 258, 263, 315
Gorham, Donald, 145
Gorman, Mike, 63
Gottfries, Carl-Gerhard, 311, 315
Gottschalk, Louis A., xviii–xix, xliii, xlv, 105–34
Green, Martin A., 75
Green, Peter, 257
Greenblatt, Milton, 17
Greenburg, Paul, 249
Greenhouse, Samuel, 195
Griffiths, Wilhelm, 35, 259
Griffiths, John, 185
Grinker, Roy, 108, 146
Guy, William, 24, 25, 293
Haase, Hans-J., 160, 291, 296
Haer, John L., 133
Hallucinogens, 154–54, 247
Halperin, Jeffrey, 230
Hambridge, Gove, 112–13
Hamburg, David, 249
Hamburger, Victor, 106
Hamilton, Max, 196
Harper, Patrick, 293, 310
Healy, David, 34, 164, 302
Heath, Robert, 58–69
Heiser, Jon, F., 126
Hill, Harris, 238
Hill, Lister, 63
Hippius, Hanns, 258
Hoff, Hans, 20
Hoffer, Abram, 27, 64, 153
See also Roche
Hogarty, Gerard, 250
Hollender, Marc, 33
Hollister, Leo E., xvii, xxxvi, xxxviii, xxxix, x, xlii, xliii, xlv, xlv, 17, 48, 135–70, 176, 209, 290
Hoyt, Harry, 53–54
Hunter, Robin, 286, 287
Huxley, Aldous, 49, 64
Huxley, Julian, 49, 64
Hydergine, xviii, 142–43. 168
Hyman, Steven, xii, 71
Imipramine (Tofranil), xix, xx, 13, 14–15, 25, 31, 69, 80–87, 89–90, 92, 96, 117, 148, 207–8, 211, 224, 244, 287, 302, 303, 304, 310
Insulin coma therapy (ICT), 20, 60–61, 64, 76–79, 83–84, 212, 278, 286, 287
sub-coma/modified, 59, 61, 78
vs. chlorpromazine, xix, 100
Iproniazid (Marsilid), xvi, 13, 20, 64, 144, 244, 271–72, 288–89, 302, 313–14
Isbell, Harris, xvi, 157, 206, 235, 236–38, 247, 261–64, 273
Isoniazid, x, 13, 144, 302
Itil, Turan M., xvi, xlii, xlv, xlv, 86, 87, 88, 89–90, 102, 171–82
Jacobson, Carlyle, 109
Jaffe, Ari B., xxi
Jaffe, Jerome, 157
Jaffe, Joseph, 75
Index

Jaffe, Milton, 156
Jamieson, Kay, 304
Janicak, Philip, 12
Janowsky, David S., xxii, xxxviii, xli, xlv, xlvii, 168, 183, 91, 286
Janssen, Paul, 150, 160, 170
Jarema, Marek, 28
Jarvik, Murray, 140, 239
Jasper, Herbert, 21
Jaspers, Karl, xii–xiii
Judd, Lewis, 185

Kahlbaum, Karl, xiv
Kahn, Renee, 261
Kalinowsky, Lothar, 12
Kalow, Werner, x
Kampov-Polevoi, Alexei B., 189
Kandel, Eric, 220
Kane, John, 230
Kaplan, Harold, 309
Karrer, Paul, 269
Katz, Ira, 310
Katz, Martin M., xxi, xli, xlv, 65, 70, 175, 176, 193–204
Kaufman, Seymour, xxxviii
Kefauver, C. Estes, 50
Kefauver-Harris amendments, 207, 248
Kellner, Robert, 304, 309
Kelso, John, 186
Kety, Seymour, 62, 195, 239, 258, 265, 314
Kielholtz, Paul, 170
Kinross-Wright, John, 3, 140, 143, 145
Klein, Donald F., xxii, xxxviii–xix., xlv, xlvii, 33, 80, 81, 82, 83, 86, 103, 205–20, 221, 223, 251, 310
Klein, Rachel Gittelman, xxii, xxxvii, xli, xlii, xliii, 210, 214, 221–31
Kleist, Karl, xv
Klerman, Gerald, xix, 65, 66, 151, 199, 250, 251, 259, 310
Klett, James, 163
Kline, Nathan S., xxxvii–xxxviii, 3, 4, 63, 68, 80, 137, 138–39, 145, 147, 164, 195, 212, 231, 271, 279, 280, 287–89, 301, 310
Koplewicz, Harold, 230
Kornetsky, Conan, xvii, xxxvii–xxxviii, xlv, 233–42
Koslow, Stephen M.
    as interviewer, 193–204
Kraepelin, Emil, xiv–xv, 28, 222, 259
Kral, Vojtech Adalbert, 26
Kramer, John, 83
Kretschmer, Emil, 171
Kretschmer, Norman, 205
Kripke, Daniel, 186
Kruijf, Paul de, 135
Kuhn, Roland, 14–15, 31
Kupfer, David, 184, 258

Laborit, Henri, 164, 278, 279
Lactate, 82, 211, 216–18, 220
Lader, Malcolm, 177
Lasagna, Louis, 195
Lasker, Mary, 63, 164
Lazar, Robert, xxi
Leckmann, James F.
    as interviewer, 221–31
Lee, Hillary, 309
Leeds, Alice, 28
Lehman, Anthony, 253
Leonhard, Karl, xv–xvi, xlv, 30–31, 300
Levine, Jerome, xxi, xlii, xlvi, xlvii, 243–55
Levinson, Douglas, 310
Lewis, Aubrey, 306
Lewis, Sinclair, 57
Liebiger, Jan, 28
Lindqvist, Margit, 160
Lipman, Ronald, 250
Lipton, Morris, 27, 252
Lisanby, Sarah H., 103
Lithium, 20, 70, 159–60, 195, 250, 294–95, 305, 312, 313
Lorazepam, 95, 101–2, 118
Lorr, Maurice, 145
Lowy, Martin, 263
Ludwig, Arnold M., xxi, 247, 248
Ludwig, Bernard, 45, 52
Lysergic acid diethylamide (LSD), xvii, xxi, 21, 70, 134, 140, 154–56, 197, 206, 239, 247–48, 253, 265, 297, 286, 315
EEG studies, 80, 84, 87
Maas, James, 203
Malitz, Sidney, 80
Malmo, Robert B., 286
Mandel, Arnold, 185
Mania, xiv, xv, xxii, 29, 58, 66, 151, 159, 168, 184, 185, 187, 191, 215, 312
and catatonia, 82, 94, 97
Manic-depressive illness, xi, xii, xiv, xv, 29, 283. See also Bipolar disorder(s)
Marshall, Wade, 110
May, Phillip, 291
McGrath, Pat, 212
McGuire, Frederick L., 126
McGuire, Jerry, 132
McNaughton, Francis, 21
Mechoulam, Raphael, 156
Mednick, Sarnoff, 181
Meduna, Ladislas, 93–94
Melancholia, xiv, xv, 31, 82, 100, 102, 104, 223, 318
Meltzer, Herbert Y., xxii–xxii, 184, 257–68
Menninger, Karl, 215, 216
Mental illness. See Psychiatric illness
Mepazine, 145, 207
Mephenesin, xvi–xvii, 41–45, 46, 49, 143
Meprobamate (Equanil, Miltown), xvii, xl, 8–10, 26, 37, 45–54, 117, 118, 143, 152, 244, 273
Merck (pharmaceutical company), 6, 15
Merlis, Sidney, 68, 80, 290
Methylphenidate, xxii, 26, 185–87, 189, 286
Meyer, Adolf, 59
Mianserin, xvii, 25, 90–91, 175, 178
Middleton, William, 144
Milano, Robert, 46
Miller, James, 49
Miller, Joseph S. A, 77, 80, 84
Miller, Laurie, 230
Minsky, Arthur, 112, 240
Möbius, Paul Julius, xi
Moises, Hans, 258
Molecular genetics, ix, xii, 35, 255
Monoamine(s), ix, xi, xxi, 187, 317, 318
Monoamine oxidase (MAO) inhibition/inhibitors, ix, xi, xxii, xxxvii, 13–14, 25, 187, 211, 271–73, 288, 301, 303, 312, 313–14
Morel, Bénédict-Augustin, xi
Morphine, xvii, 126, 220, 237–38, 242, 263–64, 258
Morris, Allen, 148
Mouchly, Saul, 244
Murphy, Dennis, 184, 258, 260, 261
Naloxone, 95, 101–2, 118, 186, 211, 220
Nasar, Sylvia, 79
Nash, John, 78
National Academy of Sciences, National Research Council (NASNRC), 61–63, 145, 236
Committee on Problems of Drug Dependence, 52, 156
Committee on Psychiatry, 6, 52
National Institutes of Health (NIH), 10, 194–95, 198, 269, 270, 271, 272, 275, 308
National Institute of Mental Health (NIMH), xii, xiii–xlv, 28, 62, 71, 99, 110–11, 112, 175, 184, 191, 211, 220, 248, 258, 265, 309
basic science emphasis, 219
Clinical Neuropharmacology Research Center (CNRC), 245–46
Clinical Research Branch, 198–99
collaborative studies, xix, 63, 65, 145, 151, 177, 194–96, 198
ECDEU program. See Early Clinical Drug Evaluation Units (ECDEU) program funding, 26, 65, 68, 82, 85, 86, 90, 98, 100, 113, 114, 181, 186, 212, 213, 238, 249, 253, 290, 308
Laboratory of Clinical Science, 239
Psychopharmacology Research Branch, 249, 251
Psychopharmacology Service Center. See Psychopharmacology Service Center (PSC)
Public Health Service. See US Public Health Service (USPHS)
National Institute on Alcohol Abuse and Alcoholism (NIAAA), 117, 126–277
National Institute on Drug Abuse (NIDA), 126, 132, 158
Neele, Edna, xv
Negative symptoms/syndromes, 8, 67–68, 124, 127, 146–47, 163, 298–99
Neuroendocrine studies, 258, 261
hypothesis of ECT, 99–101
Neuroleptic malignant syndrome, xx, 140, 258, 311
Neuroleptics, xvii, xviii, xix, xx, xxi, 5, 24, 29, 123, 239, 294, 297, 313. See also Antipsychotics
atypical, 92, 161, 263, 299
resistance, 178
threshold, 160, 163
Neuropsychiatry, 68, 76, 107–8, 111
Neuroscience, xli, 103, 18–81
Neuroses, 19–20, 47, 48, 210, 214–15, 216, 217, 247
Neurotransmitter(s), ix, xx, 55–56, 89, 91, 188, 189, 270–71, 315
Nicotinic acid, 26, 27, 64
Noce, Robert, 164–65
Noradrenalin. See Norepinephrine
Norepinephrine (NE), 25, 165, 184, 187, 188, 270, 271, 315
Nosology, xii, xiv–xvi, xx, xxxviii, xli, xlv, 30–32, 34–35, 146, 229, 315
Nyirö, Gyula, xiii, xiv, 19
Obsessive-compulsive disorder (OCD), 9, 23, 176, 219
Odejide, Bissy, 29
Olanzapine, xx, 162, 163, 263, 291, 297, 298, 300, 301
Organon (pharmaceutical company), 88–91, 175
O’Leary, James, 110
Ornstein, Anna, 112
Ornstein, Paul, 112
Orzack, Marissa, 241
Osmond, Humphry, 153
Ostow, Morton, 282
Ottosson, Jan-Otto, 99, 101
Overall, John E., xxxix, 145, 146–47, 160, 163, 166
Overstreet, David, 189
Panic disorder, xx, xxii, 82, 166, 210–11, 215–20, 224, 229, 305, 306, 312
Parkinson’s disease/Parkinsonism, xvii, 11, 44, 67
Pathophysiology, xi, 23, 214–15, 220, 224 ...
Paul, Steven M., 263
Pavlov, Ivan Petrovich, 22, 35, 109
Penfield, Wilder, 20
Pentylenetetrazol (Metrazol), xviii, 78, 142, 143, 168
Perphenazine, 4, 118–19 ...

Pethö, Bertalan, 31

Pfeiffer, Carl, 65

Pharmaceutical industry, xl, xli–xliv, xlvii, 41, 45, 47, 50, 52–54, 120, 162, 175, 206, 211, 282, 290, 292, 316

and ACNP, 17–18

conflict of interest, 104, 177, 309

and early psychopharmacology, 5–6, 63, 273–74

support/funding, 32, 33, 103, 308–9

Pharmacogenetics, ix, x–xi

Pharmacokinetics, x, xviii, xx, 30, 114, 119, 158

Pharmacological dissection, xx, xxxviii–xxxix, 208–11, 215, 251

Pharmacological heterogeneity, xii, xix, 30, 32

Phenelzine, x, xi, 13, 211, 289–90, 302

Phenothiazines, xviii, xix, xx, 4, 9, 26, 30, 123–24, 141, 145, 207, 245–46, 294, 297

Physostigmine, xxii, 168, 185–86, 190

Pi, Edward, 306

Pichot, Pierre, 33, 278

Pine, Daniel, 229, 230

Pitts, Peter, 217

Placebo, 58, 110, 181, 193, 207, 209, 211, 302–3, 304

in controlled trials, 6, 13, 65, 67–69, 81, 86, 87, 90, 92, 119, 137–38, 224, 240,

Pletscher, Alfred, xvii–xviii, xl, xlvii, 269–75

Pollack, Max, 221, 223

Positive symptoms, 67–68, 124, 127, 146–47

Positron emission tomography (PET) scanning, xxxiv, 124–25, 129–31, 134, 191, 260

Posner, Herbert, 245, 246

Prada, Miguel 286

Prakash, Rudra, 28

Prange, Arthur, 26

Premenstrual tension, 183, 184, 187

Preter, Maurice, 211

Prien, Robert, 70, 250

Prochlorperazine (Compazine), 4, 21, 24, 141

Promethazine, xvii, 172, 174, 278–79

Psychiatric illness, ix, xii–xii, xxxviii, xl, 30, 44, 49, 93, 176, 180–81, 195, 200–201, 210, 225, 244, 251

classification, xiv–xvi, 316. See also

Classification, psychiatric; Nosology

genetic aspects, xi–xii, xlvii, 255

Psychoactive drugs. See Psychotropic drugs

Psychoanalysis, xli, 19, 59, 78, 107–9, 112,

122, 205, 206, 207, 216–17, 277, 278

predominance, xxxix, 76–77, 151, 175,

187, 212–13, 316, 319

and psychopharmacology, xvii, xli, 244,

248, 261, 282–83

Psychodynamic concepts/theory. See

Psychoanalysis

Psychogeriatrics, 26, 114, 142, 144

Psychoneuroses. See Neuroses

Psychopathology, xii–xiv, xix–xx, xli, xliii, xlv,

19, 22, 15, 30, 32, 24–35, 58, 163, 175,

200, 205, 223, 228, 249, 298, 316, 318

Psychopharmacology, xix, xxxvii, xlv–xlvi,

19, 27, 29–34, 65, 85, 93, 112, 114,

116, 142, 168, 187, 195, 231, 243, 260,

265, 266, 268, 269, 313, 320

developments and challenges, xi, xlii–xlv,

37, 55, 103–4, 175, 196, 202, 271, 274,

278–82, 287, 312, 317

funding, xxxviii, 10, 32, 194

training programs, 28, 33, 186

Psychopharmacology Service Center (PSC),

68, 71, 139, 145, 151, 246–47, 248–52

Psychoses, xii–xv, xix, xlv, 21, 67, 68, 80,

142, 259, 281, 282, 303

chlorpromazine in, 7, 164

drug induced, 154–55, 262–63

heterogeneity, 222

...
methylphenidate challenge, 185
as “schizophrenia”, 77, 266
vs. anxiety, 215
Psychosomatic medicine/research, 47, 71, 112, 122
Psychotherapy, 21, 76, 77, 110, 155, 236, 304
and psychopharmacology, 20, 80, 278–79, 281, 301
Psychotropic drugs, xvii–xix, xx–xxi, xl, xlv, 26, 48, 79, 11, 141, 225, 244, 304, 307
discovery/development, ix, xii, xvii, xlvi, 29, 33, 194, 197, 259, 272–73
mechanism of action, 270–71, 313
in pre-psychopharmacology era, 20, 60, 93
studies, 23–27, 23–34, 63, 85–86, 149, 182, 239
vs. ECT, 96–98
Public Health Service. See US Public Health Service (USPHS)
Quantitative EEG, xvii, xix, xlv, 86–92, 95,
100–103, 174–75, 179-80
human vs. animal findings, 88–89
Quebec Psychopharmacological Research
Association (QPRA), 26–27
Quitkin, Frederic, 211, 212, 231
Rafaelson, Ole, 169–70, 315
Ramon y Cajal, Santiago, xiii, 286
Randomized trials (RCT), 6, 78, 207, 209, 217,
137, 140
Rapoport, Anatol, 49
Rappaport, Mark, 186
Raskin, Alan, 69, 250
Rating scales, xx, xl , xli–xliv, xlv, 66, 69, 86,
113, 145, 160, 291, 293, 311
Rausch, Jeff, 186
Reagan, Ronald, 127–29
Redlich, Fritz, 261, 262
Reiser, Morton, 135
Research Diagnostic Criteria (RDC), 199–200
Reserpine, xvii, xviii, 3, 9, 20, 49, 62, 63, 67,
117, 118, 136–42, 145, 147, 164, 206,
213, 269, 279, 280, 288–89, 300, 302
Revlon, Charles, 5
Rezvani, Amir, 189
Richards, R. K., 156
Rickels, Karl, 48, 69
Rifkin, Arthur, 231
Riggs, Douglas, 245
Rioch, David McKenzie, 77, 107, 111
Rioch, Janet, 77
Risch, Craig, 186
Risperidone, 134, 162, 263, 297, 298
Robbins, Lewis, 207, 208, 216, 217
Roberts, Richard, 139
Robins, Eli, 200
Robins, Lee, 228
Robinson, Donald S., x
Roche, xvii, 13, 51–52, 152 ...
Ross, Sherman, 65
Roth, Bryan, 260, 263
Roth, Martin, xv
Rothman, Theodore, 16–17
Rubin, Eli, 74
Rümke, Henricus Cornelis, 316
Saarma, Jüri, 28
Sachar, Edward, 217, 258
Sackler, Arthur, 206
Sainz., Anthony, 80
Sakel, Manfred, 61, 77, 69, 79
Salzman, Carl, 197
Sándor, György, 20, 32
Sandoz (pharmaceutical company), 27, 29, 80,
119–20, 260
Sargent, Will, 16
Sartorius, Norman, 29
Sarwer-Foner, Gerald J., xviii, xxxix, xliii,
277–83, 287
Saslow, George, 107
Saunders, John C., 288, 290
Saxena, Bishan, 22
Schatzberg, Alan, xix
Schering (pharmaceutical company), 4–5
Schiele, Burtrum, xxi, 4, 252
Schildkraut, Joseph, xix
Schizoaffective disorder, xx, 66
causation hypotheses, 153–54, 223, 239
carcinoid syndrome, 267
childhood asocial, xxxviii, 215, 222
dopa metabolites, 115, 116
and chlorpromazine, 37, 43, 67
genetic aspects, xi, 258
methylphenidate challenge, 185–87, 286
misdiagnoses, 66, 151
subtypes, xv–xvi, 30–31, 124, 223, 300, 312
vs. catatonia, 77, 101
Schneider, Kurt, 31
Schooler, Nina, xxi, 250, 252
Schou, Mogens, 315
Schulsinger, Fini, 181
Scott, Clifford, 282, 286
Secunda, Steve, 199
Selective serotonin reuptake inhibitors (SSRI), 91, 103, 165, 304, 305
Separation anxiety, xx, xxii, 28, 218, 223–24, 229–30
Serotonin (5-HT), xi, xvii, xxi, 162, 165, 184, 187, 188, 189, 201, 269, 270–71, 275, 315
dopamine interaction, 160, 297
Shagass, Charles, 286
Shepherd, Michael, 138, 315
Shannon, James, 68
Shore, Parkhurst, xvii, 269, 270
Shorter, Edward, 34
Simpson, George M. xxxvii, xl, xliii, xlv, 295–312
Sloan, Bruce, 287, 306, 309
Small, Saul, 245
Smith, Kline & French (SKF), 3–5, 68, 80, 137–38, 141, 142–43, 146
Smythies, John, 153
Snyder, Frederick, 258
Sourkes, Theodore, 286
Spitzer, Robert, 200, 213, 214, 293
Squibb (pharmaceutical company), 4–5, 12, 44–45, 46
Statistical methods, xli–xlii, xlv, 67, 145, 160
Stark, Louis, xli
Stein, Joseph, 75
Sternbach, Leo, 51, 272, 273
Stewart, Jon, 211, 212
Strauss, Hans, 84
Strauss, John, 258, 264
Stricknam, Claude, 6
Substance abuse, 156–57, 188, 227–28. See also Alcohol/Alcoholism, Drug abuse/Addiction
Sugerman, Arthur, 290, 296
Suicide/suicidality, xix, xxi, 12, 115, 127, 138, 183, 188, 292, 304
Sutherland, Earl, 264
Sydenham, Thomas, xiv
Szara, Stephen, 246
Szasz, Thomas, 97
Tamminga, Carol A.
as interviewer, 257–68
Taylor, Michael Alan (Mickey), xix, 82, 94, 95, 101–2
Teicher, Martin, xix
Tetrahydrocannabinol (THC), 156–58, 197
Thase, Michael, 104
Thioridazine, xxii, 65, 119–21, 148, 297
QT interval prolongation, 26–27, 121, 149, 298
Thorn, George, 59, 61
Thuillier, Jean, 278
Tobin, Joseph, 17
Tone, Andrea
as interviewer, 171–82, 269–75
Transcranial magnetic stimulation (TMS), 12–13
Tranquilizers, 16, 46, 49
major vs. minor, 123, 244. See also
Antianxiety agents; Antipsychotic agents; Neuroleptics
Tricyclic antidepressants, xix, xxxviii, 13, 14,
25, 69, 101, 102, 175, 211, 244, 301,
304, 311
vs. SSRIs, 166–67
Trifluoperazine, 5, 141
Tyhurst, James, 286
Ucha Udabe, Ronaldo, 28, 34
Udenfriend, Sidney, 270
Uhlenhuth, Eberhard H. (Uhli), 29
Ulett, George, 85, 86
US Public Health Service (USPHS), 63, 151,
157, 183
Hospital, Fort Worth, TX, 108, 110–11, 113
Hospital, Lexington, KY, 88, 101, 144, 157,
205–6, 234–35, 237–38, 242, 245,
247
Usdin, Earl, 250
Vane, Bud, 6
Van Praag, Herman M., xx–xxi, xl, xliii, xlv,
313–20
Vergara, Luis, 28
Verghese, Cherin, 308
Veterans Administration (VA), 3, 149, 162,
206, 207, 250
collaborative studies, 144–45, 147, 151, 152
hospitals, 27, 126, 189, 290
Neuropsychiatric Research Laboratory, 194
Vogel, Friedrich, x
Volavka, Jan, 100
Vossenaar, Jack, 91
Wagner-Jauregg, Julius, 75
Wallace Laboratories. See Carter Products/
Carter-Wallace
Warner, Carrie Masia, 231
Waskow, Irene, 197
Watts, Patrick, 289
Watson, James, x
Weil, Andrew, 157
Wendkos, M. H., 27
Wernicke, Carl, xiii, xv
West, Louis Jolyon (Jolly), 60, 134
Wheatley, David, 69
Whitehorn, John, 107
Whitehouse, Peter, 168
Wholberg, Gerald, 241
Wienckowski, Louis, 198
Wikler, Abraham, 88, 206, 236–37, 247,
262–63
Wilmann, Kurt, xiii
Winkelman, Nathaniel, 142–43
Winkelman, William, 282
Withdrawal effects/syndromes, xviii, xx, xxiii,
9, 77, 83, 123–24, 143–44, 152–53, 247,
292, 294, 305, 311
Wood, Barry, 107
<table>
<thead>
<tr>
<th>Name</th>
<th>Page Numbers</th>
<th>Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organizatio (WHO)</td>
<td>28–29, 33–34, 181, 201</td>
<td>Yolles, Stanley</td>
<td>198</td>
</tr>
<tr>
<td>Wortis, Joseph</td>
<td>61</td>
<td>Zeller, Albert</td>
<td>271</td>
</tr>
<tr>
<td>Wyatt, Richard</td>
<td>184, 258</td>
<td>Zilboorg, Gregory</td>
<td>277</td>
</tr>
<tr>
<td>Wyeth (pharmaceutical company)</td>
<td>9, 10, 47, 48</td>
<td>Ziprasidone</td>
<td>297, 298, 300–301</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zoch, Carlos</td>
<td>28</td>
</tr>
</tbody>
</table>


The College

The American College of Neuropsychopharmacology (ACNP), founded in 1961, is a professional organization of leading scientists. The core purpose of the College is to contribute to alleviating human suffering by advancing the dissemination of knowledge related to the biology of the brain as well as the biology, prevention, and treatment of brain disorders; by promoting emergence of pioneering young scientists as leaders within our College and within their fields of science; and by facilitating the collaboration among relevant organizations and agencies.

The Series

The 10 volumes in this series record a fifty year history of neuropsychopharmacology related by 213 pioneer clinical, academic, industrial and basic scientists in videotaped interviews, conducted by 66 colleagues between 1994 and 2008. These volumes include a preface by the series editor placing its contents in an historical context and linking each volume to the next. Each volume is dedicated to a former President of the ACNP and edited by a distinguished historian or Fellow of the College who provides an introduction to its themes and a biography of each scientist’s career. The series provides insights into a half century of discovery and innovation with its rewards and disappointments, progress and setbacks, including future expectations and hopes for the field as a whole and the ACNP as an organization.

In This Volume

In the first eight volumes of this series, interviewees reflect on their contributions to the development of neuropsychopharmacology. Volume Nine (Update) differs from prior volumes in that it includes a second interview from some of the interviewees that complements and updates the information in their first interviews. In Volume Nine, as in Volume Eight, interviewees talk about contributions to diverse areas of research and the Volume as a whole provides prime material for an overview of the changes which have taken place in neuropsychopharmacology since the 1950s. During its first fifty years neuropsychopharmacology was a rapidly moving field. Starting in the late 1950s with the gradual replacement of behavioral pharmacology by neuropharmacology, by the dawn of the 21st century, the neurotransmitter era, the first epoch in the field was coming to an end, and succeeded by a molecular genetic era, opening up a new perspective for developing pharmacological treatments. Dedicated to the memory of Nathan S. Kline, President ACNP, 1967, Volume Nine is edited by Barry Blackwell, a distinguished researcher and educator in the field. Blackwell’s report of the “cheese reaction” with monoamine oxidase inhibitors in the 1960s has had a major impact on the development of pharmacological treatment of depression.