



An Oral History Of Neuropsychopharmacology

The First Fifty Years
Peer Interviews

SERIES EDITED BY: Thomas A. Ban



Volume Eight:
DIVERSE TOPICS

EDITED BY: Carl Salzman

American College of Neuropsychopharmacology

**AN ORAL HISTORY OF
NEUROPSYCHOPHARMACOLOGY
THE FIRST FIFTY YEARS**

Peer Interviews

Volume Eight: Diverse Topics

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Thomas A. Ban (series editor)
AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

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VOLUME 8: DIVERSE TOPICS

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AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY
THE FIRST FIFTY YEARS
Peer Interviews

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Thomas A. Ban

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VOLUME 8

DIVERSE TOPICS

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VOLUME 8

Carl Salzman

DIVERSE TOPICS

Preface
Thomas A. Ban

Dedicated to the Memory of Milton Greenblatt, President ACNP, 1964

PREFACE

Thomas A. Ban

In each of the first seven volumes in this series interviewees reflect on their contributions to a particular area of research in neuropsychopharmacology.* Thus, in each volume the story of neuropsychopharmacology is told from a different perspective. In Volume Eight, interviewees talk about their contributions on diverse topics. Presentation of these many stories does not focus on any particular area of research. Yet, the volume as a whole mirrors the changes which have taken place in the entire field in fifty years.

The Preface to Volume Eight also differs from the Preface to the other volumes. In all other volumes the first part of the Preface provides background information to interviewees' research contributions, placing the contributions into a historical context. For the interviews in Volume Eight such background information may be found in prior volumes. Instead, in the first part of the Preface, the larger framework of the development in neuropsychopharmacology that has been the subject of this series is discussed.

Regulation

One of the essential prerequisites for neuropsychopharmacological research is the availability of psychotropic drugs with known therapeutic effects. During the 1950s several drugs were introduced by the pharmaceutical industry for the treatment of schizophrenia, depression, mania and anxiety disorders. Yet, it was not before the 1960s that approval of drugs for specific indications in clinical use, based on demonstrated efficacy, became a requirement in the United States.

The first Pure Food and Drug Act in the United States, was introduced in 1906,¹ but until the early sixties all regulations were related to safety requirements, and to the separation of prescription drugs from over the counter medications. The scope of legislation was extended in 1962 with the enactment of the Kefauver-Harris Amendment (KHA),** which stipulated that: the effectiveness

* Volume One: Starting Up (behavioral 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).

** In addition to safety and efficacy, the KHA also stipulates that (1) drugs have to be produced in accordance with sound manufacturing practices; (2) the distribution and the use of investigational drugs have to be adequately controlled; (3) prescription drug labelling and advertising have to conform to governmental approval; and (4) provision has to be made by the manufacturer (distributor) for keeping records and reporting on the distribution and feedback of approved drugs, so that an ineffective or unsafe drug could be removed from the market, or its directions for use revised.

as well as the safety of a new drug has to be established before the drug is released for clinical use.²

Extension of the legislation from proof of safety to efficacy has had a major impact on clinical research with psychotropic drugs. It has also led to the implementation of structured clinical drug development in three successive phases. Phase I, “human pharmacology” starts when the new drug is first given to man, usually to normal subjects. Its purpose is the determination of the drug’s preferred route of administration and safe dose range. Phase II, “clinical pharmacology” includes the initial clinical trials for the treatment of a specific disease, or prophylactic purposes. Phase III, “clinical investigation” provides information on the efficacy, safety, optimum dose range and schedule of administration of the drug.

The single, most important influence on pharmacotherapy is the regulation that defines the requirements for approval of a new drug on prescription. To meet requirements of the US Food and Drug Administration (FDA), a drug must show a statistically significant difference (superiority) to placebo in two pivotal double-blind, randomized clinical trials which are of adequate sample size and statistical power. Furthermore, to meet the requirement that an ineffective or unsafe drug could be removed, the three-phase clinical development was supplemented with drug surveillance (Phase IV).

A resolution of the National Advisory Health Council in 1965 led to the establishment of Institutional Review Boards (IRBs). It also helped build the clinical framework in which research with psychotropic drugs, operates. IRBs are to approve proposed research. Their primary objective is to ensure the safety of experimental subjects (ES) involved in the research. In 1966, the Surgeon General of the United States issued a policy statement in which various methods were listed to safeguard humans involved in National Institutes of Health (NIH) or more generally Public Health Service (PHS) supported research. Special policies were formulated for controlled experiments.

In 1966 the FDA amended its regulation with a statement of policy formulated by Goddard. The “Goddard Amendment” stipulated that whenever an investigational drug is used in human beings the investigators should obtain informed consent from the ES.³ At the time the Goddard amendment was introduced it served exclusively the protection of patients but by the time of the 1980s it became a protective shield (from litigation) for studying new drugs developed by drug companies. The amendment has had an impact on breaking the old paternalistic style of doctor–patient relationship. It also opened the path for “medical ethics” to play a steadily increasing role in medical universities.

Ethics

Human experiments have been instrumental in the development of medical skills. Yet, until the mid-20th century human experiments were not controlled by legislation but by the informal code of approval of the scientific fraternity. In the middle of the 19th century, Claude Bernard, in his *Introduction to Experimental Medicine*, asserted that “it is the duty and the right of the physician to perform an experiment on man whenever it can save his life, cure him, or gain him some personal benefits”. But, Bernard also insisted on “never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science”.⁴ The first systematic presentation of the ethics on experimentation in humans was drawn up by the Nuremberg Military Tribunal after World War II, and published in 1947, in a legal document, the Nuremberg Code. The gist of the “laws” incorporated in this document are: (1) the ES must give voluntary (informed) consent prior to being included in an experiment; (2) the experiment should yield fruitful results for the good of society, and its results should not be attainable by any other means; (3) the experiment must be based on prior animal studies and knowledge of the natural history of the disease; (4) the degree of risk involved in the experiment should not exceed the potential benefits of the research for society; (5) the ES should be at liberty to bring the experiment to an end.⁵

The principles of the Nuremberg Code were revived in 1955 by the United Nations Third Committee on Social, Humanitarian and Cultural Questions, and incorporated in 1964 in the Helsinki Declaration (HD), based on the Declaration of Geneva of the World Medical Association, and the International Code of Ethics. The Helsinki Declaration emphasizes that the “responsibility for clinical research always remains with the research worker,” and “it never falls on the (experimental) subject”.⁶ The Declaration has been endorsed by several nations and numerous medical associations; the Judicial Council of the American Medical Association recommended its adoption in 1966 at the annual convention of the Association.

During the second half of the 20th century clinical studies with psychotropic drugs have become a large component of research in which human subjects are involved. To meet fully the obligations of ethical conduct, the “fruitful results for the good of society,” must be *disseminated*, and *integrated* with the existing body of knowledge. Within our societal structure, it is the task of *marketing* to disseminate the findings in clinical research, and it is the responsibility of education to integrate the new information with existing knowledge.

Marketing & Education

In the 1950s, the pharmaceutical industry was not ready for the dissemination of the rapidly growing body of information on psychotropic drugs. (See, Berger Volumes 3 & 9.) Means of communication were scarce. The first journal in neuropsychopharmacology, *Psychopharmacologia*,⁷ was launched in 1958 by Ernst Rothlin, the founding president of CINP, and Abraham Wikler, and the second, *International Journal of Neuropharmacology*,⁸ (now, *Neuropharmacology*), was founded in 1961 by Bernard Brodie, Erminio Costa, Silvio Garattini, and Corneille Radouco-Thomas, one of the founders of CINP, with Costa and Radouco-Thomas, as founding editors-in-chief. (See, Costa Volume 7 and Garattini Volume 3.) In 1966, to overcome the difficulties in communication of information on psychotropic drugs, a World Health Organization Scientific Group on Research in Psychopharmacology recommended the development of an International (Collaborative) Reference Centers Network in Psychopharmacology (IRCNP). The IRCNP was launched in 1968 with regional and national reference centers around the world; its activities were coordinated by Alice Leeds from the Psychopharmacology Research Branch of the NIMH in Rockville.^{9,10} Supported by NIMH, IRCNP published and distributed its journal, the *Psychopharmacology Bulletin*, with free copies to Universities. It also compiled an *International Directory of Investigators in Psychopharmacology*, including their names, addresses, affiliations and field of research, and developed an index card system for the collection of data on the efficacy, safety and mechanism of action of psychotropic drugs.¹¹ In the same year as IRCNP was launched, the first data bank for clinical investigations was established in Washington DC, at George Washington University. (See, Preface Volume 4 and Overall Volume 4.)

As time passed, industry developed the necessary marketing arms required to disseminate the information about their psychotropic drugs. By the 1980s the IRCNP withered away.

The objective of industrial marketing is to capture the largest possible market for a substance, by persuading physicians to prescribe the drug. Industry is free to support research in order to generate findings that would attract attention to a substance or trigger speculations about possible advantages in prescribing it. The only limitation of marketing is that it has to adhere to the labelling and advertising approved by the FDA in the United States. Yet, by sponsoring studies using electrophysiological, biochemical, neuroimaging, molecular genetics, and other advanced technologies in psychiatry, industrial marketing has had a major impact on the development of neuropsychopharmacology. It was also instrumental in transforming psychiatry, dominated by psychodynamics in the United States, into a medical discipline. Without this support, the

replacement of the old cadre of psychoanalysts, with neuropsychopharmacologists, at the helm of psychiatric departments would have taken longer.

Parallel with the changes in Psychiatry, the role of psychiatrists in the drug industry has changed from advisors on issues which required psychiatric knowledge in the 1960s and '70s, to leaders of teams that generate the evidence in clinical investigations for regulatory approval of drugs in the 1980s. . By the 1990s, psychiatrists working in the employment of industry were moving back and forth between industry and academy. They had become key players in the generation of information on which both, education in pharmacotherapy and marketing of psychotropic drugs, is based.

The signal difference between marketing and education is that marketing is focused on a drug with the objective of getting a particular product prescribed, whereas education is focused on the patient with the objective of selecting for each individual the optimal treatment by the discriminate use of available drugs. While sophisticated marketing tries to guide physicians to prescribe a particular product or give preference to a group of products in treatment, proper education equips physicians with the know-how to evaluate and integrate new information with the existing body of knowledge. At the core of education is the the translation in information from preclinical research, which sets the stage for the clinical development of a psychotropic drug, and from clinical investigations upon which the prescribing of the drug in clinical practice is based. In the evaluation of pre-clinical information the focus is on the separation of findings from interpretations. Findings are established relationships between research results in different areas of the field usually derived by hypotheses testing, whereas interpretations are assumed relationships prone to the fallacies of formal logic. In the evaluation of clinical information, the focus is on the recognition of the clinically relevant findings hidden behind statistically significant results. Without information on the "effect size," "t" values, response rates, etc., the "p" values ¹² of statistical analyses indicate only the level of confidence, the probability that there is a treatment responsive group within the population studied. (See, Preface Volume 4.)

A division of labor has evolved in introducing new drugs during the past fifty years. It is based on a model in which it is the task of (governmental) regulatory bodies to ascertain that the drug released for clinical use is effective and safe, relative to the risk of the disease itself; the task of industrial marketing is to disseminate information on the drug and to generate interest in prescribing it; and the task of (academic) education is to provide the necessary teaching so that the drug is prescribed in a discriminative manner. The confounding of roles and functions in this model has led to conflicts of interest and interfered with the optimal use of psychotropic drugs. It was also counterproductive for neuropsychopharmacological research.

Conflict of Interest

Prior to the 1980s, little attention was paid to “conflict of interest” in science and medicine.^{13,14} At present authors, in most medical journals, and speakers, at most medical conferences, are required to disclose their financial involvement with the pharmaceutical industry.¹⁵ By focusing on financial motivation current policies have distracted attention that in neuropsychopharmacology, a discipline in which pharmacological homogeneity of psychiatric populations is prerequisite for progress, the conflicting motivations (objectives) of marketing with education has interfered with the development of rational pharmacological treatment.

Introduction of psychotropic drugs, during the 1950s, focused attention on the pharmacological heterogeneity within psychiatric diagnoses.¹⁶ There was a need to resolve this heterogeneity by developing a pharmacologically valid classification of mental illness.¹⁷ To date, this has not happened..¹⁸ Instead, to meet marketing needs, the randomized clinical trial was adopted for the demonstration of efficacy in pharmacologically heterogeneous diagnostic populations.¹⁹ The problem became compounded in the early 1990s, with the replacement of single-center isolated clinical studies by multi-center centrally coordinated clinical investigations. Many of these studies are designed for the purpose of registration by regulatory authorities and for supporting possible advantages of new drugs. Moreover, the data collected in most of these studies are propriety and communication, based on analyses of these data, is controlled by sponsoring drug companies. Since the findings of this research provide the evidence base for both, marketing and education, by the end of the 20th century, information related to the pharmacotherapy of mental illness has become controlled by the drug industry.

Today, most “evidence-based” information is generated in multi-center studies and serves the purpose of guiding physicians to prescribe one or another psychotropic drug, or group of drugs. Treatment guidelines, prepared by opinion leaders and endorsed by professional societies are no exceptions.²⁰ By disqualifying papers from the first thirty years of pharmacotherapy on grounds of methodological shortcomings, and summarizing findings in studies designed to create a market niche for each newly introduced drug, guidelines, task force reports, and experts’ reviews inadvertently justify the preferential prescription and inclusion in national drug formularies the newest and most expensive drugs.²¹

The blurring of education and marketing in the communication of “evidence-based” information has encouraged educators in pharmacotherapy to pursue activities in conflict with their fiduciary interest. Addressing violations which arise from this confound as ethical, distracts attention from the heart

of the issue that until the pharmacological heterogeneity within the diagnostic groups is resolved pharmacotherapy, with psychotropic drugs will remain prone to one sided, marketing input and interests. Furthermore, with pharmacologically heterogeneous diagnoses the pharmacodynamic information generated by neuropharmacological research can be related only to the side effect profile of psychotropic drugs.

It is within this framework that the research and educational activities of interviewees took place in Volume Eight and in all other volumes of this series.

Interviewees & Interviewers

Volume 8 includes transcripts of 24 videotaped biographic interviews with 19 psychiatrists, 2 basic scientists (Koslow and Maickel), one neurologist (Kleinman), one internist/clinical pharmacologist (Ackenheil), and one clinical psychologist (Frank). All but two of the interviewees (Ceskova and Gaszner) are affiliated with ACNP; and five (Charney, Coyle, Davis, Nemeroff and Shader) are past-presidents of the College.

The interviews were conducted in a period from 1997 to 2008, and with the exception of two, at the annual meeting of the College. One of these two interviews, Ceskova's was done at CINP's biennial Congress in Paris (France), and the other, Shader's was conducted at Tufts University (his work place,) in Medford, Massachusetts.

The 24 interviewees were interviewed by 13 interviewers. Eleven of the interviewers are peers of the interviewees, and 2, Braslow and Tone, are medical historians. (Braslow is also a psychiatrist.) From the 13 interviewers, 4 conducted more than one interview: Tone conducted seven, Ban four, and Hollister and Bunney two each.

By the time the editing of Volume Eight was completed, 3 of the interviewees (Ackenheil, Maickel and Tollefson), and 1 of the interviewers (Hollister) passed away.

Contributions of Interviewees

Four of the interviewees (Ackenheil, Maickel, Cole and Koslow) are first, second and third generation representatives of **Brodie's school** (at NIH), where development of neuropsychopharmacology began. (See, Preface and Introduction Volume 3.) *Roger Maickel*, a disciple of Bernard Brodie himself (from 1958 to 1965) was among the first in the 1960s to use drugs with known effects on biogenic amine systems as "tools" to examine neuronal processes involved in the response of the hypothalamus-pituitary-adrenocortical system to cold exposure (in the rat).²² His research in the 1980s contributed to opening

the path for neuropharmacological studies in stress.^{23,24,25} In the 1960s Maickel, in collaboration with Frank Miller and Ray Cox, developed a procedure for the extraction of monoamines from the rat brain, and spectrophotofluorimetric assays for the determination of norepinephrine (NE), serotonin (5-HT), and the 5-HT metabolite, 5-hydroxyindole acetic acid (5-HIAA).^{26,27}

Manfred Ackenheil was a fellow of Norbert Matussek, one of the German disciples of Brodie, in Hanns Hippus' Department of Psychiatry at Ludwig Maximilians University, in Munich. (See, Hippus Volume 1.) He was a member of Matussek's team that showed that in humans, the growth hormone (HGH) response to clonidine, a postsynaptic α -receptor agonist, is significantly reduced in patients with endogenous depression compared to normal subjects, and patients with schizophrenia and neurotic depression.^{28,29,30} Ackenheil's theory that clozapine differs in its mode of action from the other neuroleptics by its predominant effect on mesolimbic dopamine structures, was one of the first steps in a chain of events that led to the dividing of antipsychotics in the 1980s into "atypical" and "typical" neuroleptics.^{31,32} Ackenheil and Matussek, were first to offer a psychopharmacology program in a university department of psychiatry in Germany.³³

Stephen Koslow was a fellow at National Institute of Mental Health (NIMH), in the laboratory of Erminio Costa, a disciple of Brodie. (See, Costa Volume 7.) In the 1970s he developed, in collaboration with Flaminio Cattabeni, a method to measure indolalkylamines in the pineal gland of the rat, using multiple ion detection with mass fragmentography.^{34,35} In the 1980s Koslow contributed to the information on the cerebrospinal fluid (CSF) and urinary concentration of biogenic amines and their metabolites in depression and mania.³⁶ In the 1990s his interest shifted to neuroinformatics.³⁷ By setting up data bases from his position at NIMH that would allow access to all information generated in neuroscience for analyses, Koslow helped open up a new perspective for research and education in neuropsychopharmacology.³⁸

Joseph Coyle, a student of Solomon Snyder, was a fellow in the laboratory of Julius Axelrod, a disciple of Brodie. (See, Axelrod and Snyder Volume 3.) By embracing classical enzymology, immunochemistry, ligand binding and molecular biology, his research reflects the rapid advances in technology during the last quarter of the 20th century. Coyle's separation of the dopamine transporter from the norepinephrine transporter in the late 1960s was instrumental for the demonstration of dopamine receptor blockade with neuroleptics.^{39,40,41} Coyle was first to show that antiparkinson drugs inhibit dopamine uptake in the corpus striatum.⁴² Central to Coyle's research is the role of glutamate in brain development and psychopathology.⁴³ In the 1980s he demonstrated that a selective lesion of the nucleus basalis, produced by the injection of glutamate agonists, resulted in cholinergic deficit, similar to that seen in Alzheimer's

disease (AD)⁴⁴ and hypothesized that in the pathomechanism of AD, over-activation of N-methyl-D-aspartate (NMDA) receptors by glutamate plays a role.⁴⁵ Coyle's hypothesis triggered research that contributed to the introduction of memantin (Namenda,) a substance that blocks NMDA receptors and prevents the effect of glutamate on the receptor, in the treatment of AD.⁴⁶ By producing a lesion of striatal neurones with kainic acid, Coyle developed an animal model for Huntington's chorea,⁴⁷ and by producing a selective lesion in the brain by methaoxymethyl acetate (MAM), he developed an animal model for schizophrenia. The schizophrenia model is based on the assumption that NMDA receptor hypofunction is at the core of the disease.⁴⁸ In the 1990s, Coyle became the Founding Chairman of Harvard's Consolidated Department of Psychiatry, and editor-in-chief of the *Archives of General Psychiatry* of the American Medical Association.

Seven of the interviewees (Ebert, Charney, Heninger, Henn, Mandell, Mathé, and Nemeroff), have contributed to the re-evaluation of diagnostic concepts in psychiatry with the employment of **biological measures**. They have also contributed to the transformation of psychiatric education from psychoanalytical to biological during the 1960s, 70s, 80s and '90s. Of special importance in this respect was *George Heninger's* contribution; at least six future departmental chairmen of psychiatry in the United States - Dennis Charney, Pedro Delgado, David Kupfer, Christopher McDougel, Eric Nestler and Thomas Uhde - were trained in his unit at Yale. In the 1960s Heninger had shown diurnal variations in cerebral evoked responses.⁴⁹ Subsequently, in the 1970s, with the use of spectral analysis, he revealed correspondence between the therapeutic and the evoked response to treatment with lithium in manic patients.⁵⁰ There was no correspondence between the therapeutic and evoked response to treatment with chlorpromazine in schizophrenia.⁵¹ Heninger was first in the mid-1970s to report on interspecies differences in metabolizing lithium, with cats closer to human than rats and monkeys closer than cats. His finding of differences in somatosensory evoked responses between the rat and the cat invalidated findings of many years of lithium research, including some of his own findings.⁵² In the early 1980s Heninger was also among the first to report on lithium augmentation of antidepressant treatment in refractory depression.⁵³ In the 1990s he was member of research teams which studied the effect of fluvoxamine on yohimbine-induced anxiety and panic disorder,⁵⁴ the role of serotonin in the neurobiology of depression,⁵⁵ and the effects of ketamine on depression.⁵⁶ In 1997, together with Duman and Nestler, Heninger proposed a molecular and cellular theory of depression.⁵⁷

In 1981, *Dennis Charney* published on the role of changes in receptor sensitivity in the mechanism of action of antidepressants.⁵⁸ In 1982, he was among the first to show that combined administration of naltrexone

and clonidine is a safe, effective and rapid treatment of abrupt withdrawal from methadone.⁵⁹ Charney was member of the team that demonstrated a reduction of hippocampal volume, as measured by magnetic resonance imaging, with a decrease of hippocampal based memory function in post-traumatic stress disorder (PTSD).^{60,61,62,63} They also showed hippocampal volume reduction in major depression, and increase of hippocampal volume with corresponding changes in memory function after the administration of serotonin re-uptake inhibitors.⁶⁴ The findings of Charney's team with the employment of positron emission tomography (PET) and functional MRI, point to the involvement of ventral prefrontal-striatal-structures in the pathophysiology of bipolar disorder,⁶⁵ and with morphometric measures indicate a prominent decrease in amygdala volume in both adolescent and adult bipolar patients.⁶⁶ In the early years of the 21st century, Charney was among the first to study the antidepressant effect of ketamine⁶⁷ and the effectiveness of an N-methyl-D-aspartate antagonist in the treatment of depression.⁶⁸

In the 1960s, *Arnold Mandell* reported induction of hepatic tryptophan pyrrolase activity with elevated urinary corticoid excretion, cleavage of the indole ring, and marked reduction of urinary serotonin metabolites in depression.^{69,70,71} He also demonstrated changes in plasma corticosteroid concentration after electrical stimulation of the hippocampus and amygdala.⁷² In the 1970s, in collaboration with Segal, Mandel showed behavioural activation in rats during intraventricular infusion of norepinephrine,⁷³ and progressive motor activation with an increase of stereotypies during long-term administration of d'amphetamine.⁷⁴ And, in collaboration with Knapp he defined the role of high affinity uptake of tryptophan into serotonergic neurons in the regulation of serotonin biosynthesis in the brain,⁷⁵ and demonstrated the effect of narcotic drugs on serotonin biosynthetic systems.⁷⁶ In 1978, Mandell suggested that in the regulation of tyrosin and tryptophan hydroxylase activity "redundant mechanisms" are involved in the brain.⁷⁷

In the late 1970s, *Michael Ebert* developed a technique for cannulating the lateral ventricle for continuous collection of CSF in monkeys. He also established with his team that only about one fifth of urinary MHPG is derived from the CNS.⁷⁸ In a series of studies conducted in eating disorders in the 1980s Ebert and his associates found higher levels of cerebrospinal fluid opioid activity,⁷⁹ irregularities in CNS monoamine metabolism,⁸⁰ and abnormalities in plasma and cerebrospinal fluid arginine and vasopressin, in patients with anorexia nervosa.⁸¹ They also found a decrease in calorie intake in normal weight patients with bulimia,⁸² and lower indices of 5-HT turnover rate in the brain of anorexic patients with bulimia, than in anorexic patients without bulimia.⁸³ In the 1990s Ebert was involved in measuring the corticotrophin – releasing

hormone, norepinephrine, MHPG, 5-hydroxyindoleacetic acid, and tryptophan in the CSF of alcoholic patients.⁸⁴

Aleksander Math was first to demonstrate that prostaglandins play a role in the pathogenesis of asthma.⁸⁵ He was also among the first to show changes in some prostaglandins in the CSF of patients with schizophrenia.⁸⁶ Mathé's demonstration with Jeanette Miller of lithium's effect on early gene (cFos,) expression⁸⁷ has opened up a new avenue in the study of lithium's mode of action.

Charles Nemeroff's research focused on the detection of changes in psychiatric disorders that might provide targets for rational pharmacological treatments. One such target he identified was the corticotropin releasing factor (CRF) that he found elevated in depression.^{88,89,90,91,92} He had also shown that early life stressors⁹³ and child abuse may lead to an elevation of CRF.^{94,95} Since injection of CRF into the brain of animals produced behavioral changes similar to those seen in depressive and anxiety disorders in human, Nemeroff has suggested the development of CRF antagonists for the treatment of depression and anxiety.^{96,97} Nemeroff was member of the team that reported on a novel transgenic mouse for gene targeting within cells that express cCRF.⁹⁸ In another line of research Nemeroff found increased neurotensin gene expression in the striatum with "typical," and in the nucleus accumbens with "atypical" antipsychotic drugs.^{99,100, 101} Assuming that the increase in neurotensin gene expression in the striatum might be predictive of liability for developing EPS, whereas the increase in neurotensin gene expression in the nucleus accumbens might be predictive of therapeutic efficacy, Nemeroff has raised the possibility that neurotensin receptor agonists might represent a novel class of antipsychotic drugs.^{102,103}

Fritz Henn's discovery, in the early 1970s, that astrocytes have high affinity glutamate and GABA uptake systems, opened up a new area of research that led to studies on the role of the glutamatergic system in mental disorders.¹⁰⁴ In another line of research Henn was first to show that neurogenesis in the hippocampus is related to stress and unrelated to depression.¹⁰⁵ In collaboration with B Vollmayr, he introduced two "out bred lines of rats" for depression research: the congenitally helpless strain and the resilient line,¹⁰⁶ and he was member of the team that studied sensory information processing in neuroleptic naïve first episode schizophrenic patients with the employment of functional magnetic resonance imaging.¹⁰⁷

Two of the interviewees (Kenneth Davis and Kleinman) were involved in research using material from **brain banks**. *Joel Kleinman*, working in the brain bank he established at NIMH, identified potential susceptibility genes for schizophrenia.^{108,109} He was member of the teams that reported on a primate-specific brain isoform of KCNH2 that affects neuronal repolarization and risk for schizophrenia,¹¹⁰ and found that DISC1 splice variants are upregulated

in schizophrenia.¹¹¹ Kleinman's research with Daniel Weinberger implicated DARP-32 in human fronto-striatal cortical structure function and cognition.¹¹² (See, Weinberger Volume 2.)

In the mid 1970s, selective loss of cholinergic neurons was reported in Alzheimer's disease¹¹³ and *Kenneth L. Davis* demonstrated that physostigmine, a cholinesterase inhibitor, improved learning in normal subjects.¹¹⁴ He followed up these findings and in the '80s showed enhancement of memory processes in Alzheimer's disease with multiple-doses of intravenous physostigmine.¹¹⁵ Davis' findings contributed to the revival of interest in tacrine,¹¹⁶ and to developing cholinesterase inhibitors for the treatment of AD. (See, Gershon Volume 1.) In an entirely different area of research, Davis and his associates found dysregulation of myelination¹¹⁷ associated with white matter changes in schizophrenic brains.¹¹⁸

One of the interviewees, *Paul Leber* contributed to the shaping of **drug regulation** relevant to the approval of psychotropic drugs for clinical use in the 1980s and '90s; his efforts had a great impact on clinical drug development and teaching of pharmacotherapy with psychotropic drugs. Leber, a pathologist and psychiatrist in the employment of the FDA, spearheaded the implementation of the double-blind, placebo-controlled randomized trial (RCT) in the clinical development of psychotropic drugs and advanced the view that only RCTs with a placebo arm could provide unambiguous findings about efficacy.¹¹⁹ He emphasized the "threats" that the employment of "enrichment strategies" in sample selection represents,¹²⁰ and the "hazards" of making "inferences" about clinical applications from statistical probabilities^{121,122} He also addressed special methodological issues related to clinical investigations designed for showing changes in the progression of Alzheimer's disease.¹²³

Two of the interviewees (*Beasley* and *Tollefson*) worked for **pharmaceutical companies** for some time during their professional career. *Garry Tollefson* led Eli Lilly's team in the early 1990s that developed and launched olanzapine for the treatment of schizophrenia.^{124,125,126} Prior to joining Lilly, Tollefson, developed an erythrocyte model for studying the effect of drugs on muscarinic receptors.^{127,128}

Charles Beasley led Eli Lilly's Phase IV team of fluoxetine which revealed that the frequently encountered "activation" and occasional "paradoxical sedation" in the course of treatment is dose dependent.^{129,130} He also reported on possible interaction between fluoxetine and monoamine oxidase inhibitors.¹³¹ In the 1990s, in response to reports of suicide attributed to fluoxetine, Beasley coordinated the analysis of information in controlled clinical trials that "failed to support the hypothesis of increased suicidality" with the drug.^{132,133} He also participated in clinical studies with olanzapine in the treatment of schizophrenia.¹³⁴ Prior to joining Lilly, Beasley was among the first to report that a blunted

TSH response in the TRH stimulation test is predictive of responsiveness to haloperidol.¹³⁵

Three of the interviewees (Frank, Gaszner and Judd) were engaged in research related to **affective disorders or antidepressants**. In the 1970s, *Lewis Judd* demonstrated that chronic administration of lithium to normal subjects has a slowing effect on cognition. He also showed that pre-treatment with lithium has a “dampening effect” on symptoms of experimental intoxication with cocaine and alcohol.^{136,137} In a 12 year prospective study Judd and his associates found that patients with unipolar depression are ill 60 percent, and asymptomatic less than half of their lifetime.¹³⁸ They also reported that full recovery from a manic or depressive episode without residual symptoms is predictive of good prognosis.^{139,140}

In a series of studies conducted in the early 1980s in normal subjects, *Peter Gaszner*, in collaboration with Elemer Szabadi and Christopher Bradshaw, demonstrated differences in peripheral anticholinergic activity among tricyclic antidepressants.^{141,142} They had also shown adrenergic blocking effect with neuroleptics.¹⁴³ In the 1990s, Gaszner was a member of the international team which demonstrated the efficacy of reboxetine in major depression.¹⁴⁴ In collaboration with Thomas Ban, he developed a composite diagnostic evaluation to study the therapeutic profile of drugs used in the treatment of mania.¹⁴⁵ (See, Ban Volumes 4 & 9.)

Ellen Frank, in collaboration with David Kupfer contributed information on the effectiveness of maintenance therapy with antidepressants.¹⁴⁶ (See, Kupfer Volume 7.) She was a member of the team which developed in the early 1990s consensus definitions for terms used in clinical studies with psychotropic drugs, such as response, remission, recovery, relapse and recurrence.¹⁴⁷ Frank with her associates reported on disruption of social rhythm at the onset of a unipolar or bipolar affective episode.¹⁴⁸ She also explored the usefulness of interpersonal and social rhythm therapy of bipolar I disorder,¹⁴⁹ and of individual psychotherapy and pharmacotherapy with SSRIs of depression.¹⁵⁰

Five of the interviewees (Ceskova, Glick, Salzman, Shader and Stahl) were intensively involved in **educational activities** with psychotropic drugs. Based on a series of clinical studies *Ira Glick* reported that psychoeducational family intervention (PEFI) did not compensate for using neuroleptics in an inadequate dose in the treatment of schizophrenia¹⁵¹; that only in psychotic patients with bipolar disorder could family therapy improve the outcome of pharmacological treatment¹⁵²; and that “working with the families” of hospitalized schizophrenic, bipolar and unipolar depressed patients, added to the effectiveness of pharmacological treatment.¹⁵³ In 2009 Glick recommended the reintegration of family therapy training in psychiatric residency training programs.¹⁵⁴ In collaboration with David Janowsky, Carl Salzman and Richard Shader, Glick developed

a “model” psychopharmacology curriculum for psychiatric residents.^{155,156,157} (See, Janowsky Volumes 5 & 9.) Glick was also involved in studying the effect of several factors on treatment outcome, e.g., duration of hospitalization,¹⁵⁸ combining pharmacological with psychological treatment.¹⁵⁹

Richard Shader was a member of the team that developed the model curriculum for teaching psychopharmacology in 1993. In the late 1960s, Shader was first, with DiMascio, Salzman and Harmatz, to report on hostility induced by some benzodiazepines, e.g., chlordiazepoxide.^{160,161} During the 1970s, in collaboration with David Greenblatt, Shader contributed to knowledge on the pharmacokinetics of various benzodiazepine drugs.^{162,163} Shader and Greenblatt also co-authored a book, published in 1974¹⁶⁴ and a paper, published in 1981, on benzodiazepines in clinical practice.¹⁶⁵

Carl Salzman was also a member of the team that developed the model curriculum and as a Harvard professor of psychiatry he was instrumental in implementing the curriculum. Involved with Richard Shader in research with benzodiazepines, Salzman became chairman of APA’s Task Force that reported on benzodiazepine dependence, toxicity and abuse.¹⁶⁶ In the 1990s Salzman’s focus of interest shifted to geriatric psychopharmacology^{167,168} and he became involved in clinical investigations with psychotropic drugs in the aged.^{169,170} (See, Preface Volume 7.) In the mid-1990s Salzman and his associates published findings on the effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder.¹⁷¹

In the 1980s and ‘90s *Eva Ceskova*, conducted clinical investigations with various neuroleptics, e.g., haloperidol, risperidone^{172,173}. In the early years of the 21st century her research switched to explore the use of biological measures in the assessment of changes in the course of treatment with neuroleptics,^{174,175} and in the prediction of treatment response.^{176,177,178, 179}

Stephen Stahl, a disciple of Herbert Meltzer, used in the mid-1970s the platelet as a diagnostic tool for the study of biogenic amines in psychiatric and neurologic disorders.¹⁸⁰ (See, Meltzer Volumes 5 & 9.) In 1976 he co-authored with Meltzer one of the first reviews on the dopamine hypothesis of schizophrenia.¹⁸¹ As the founding chairman of the Neuroscience Education Institute in San Diego, Stahl was involved in teaching pharmacotherapy with psychotropic drugs to psychiatrists, primary care physicians and nurse practitioners world wide. In his *Essential Psychopharmacology* and some of his other publications,^{182,183} he advocates the “preventive” use of psychotropic drugs, e.g., the use of β -blockers immediately after trauma to block the rise of norepinephrine to prevent post-traumatic stress disorder. In 1999 Stahl suggested the combining of clinical experience with guidelines in the selection of an atypical antipsychotic drug for the treatment of schizophrenia.¹⁸⁴ Stahl was a member of the

team that proposed adding olanzapine or other atypical antipsychotics as an augmentation strategy in treatment resistant major depression.¹⁸⁵

As in all prior volumes, interviewees included in Volume 8 entered the field at different stages in the development of neuropsychopharmacology. Probably because of the diverse topics, Volume 8 reflects more than any of the prior volumes the emergence of a new psychiatry in which NPP plays a prominent role. Carl Salzman, the editor of this volume, distinguished himself as a leader of education in NPP in the United States.

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ABBREVIATIONS

AAAS	American Association for the Advancement of Science
ACNP	American College of Neuropsychopharmacology
ACTH	adrenocorticotrop(h)ic hormone
AD	affective disorders
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
AI	artificial intelligence
AIDS	autoimmune deficiency disease
ALS	amyotrophic lateral sclerosis
AMP	adenosine monophosphate
AP	activator protein
APA	American Psychiatric Association
APP	Alzheimer pre-protein
ASPET	American Society for Pharmacology and Experimental Therapeutics
ATM	automated teller machine
ATP	adenosine triphosphate
B-25	air-plain WW-II
BDNF	brain derived neurotrophic factor
benzo	benzodiazepines
BUSM	Boston University School of Medicine
CA	California
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBT	cognitive behavioral therapy
CDZ	chlordiazepoxide
CEO	chief executive officer
cFos	(an early gene expression)
CGRP	calcitonin gene related peptide
CINP	Collegium Internationale Neuro-Psychopharmacologicum
CME	continuous medical education
CNS	central nervous system
CODE	Composite Diagnostic Evaluation System
CODE-DD	Composite Diagnostic Evaluation for Depressive Disorders
CODE-HD	Composite Diagnostic Evaluation for Hyperthymic Disorders
COMT	catechol-O-methyltransferase
CPZ	chlorpromazine
CRC	clinical research center
CRF	corticotrophin releasing factor

CRH	corticotropin releasing hormone
CSF	cerebrospinal fluid
CT	Connecticut
CVA	cerebrovascular accident
d	dextro
D	dopamine receptor
DA	dopamine receptor antagonist
DBH	dopamine- β -hydroxylase
DMT	dimethyltryptamine
DNA	deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of the American Psychiatric Association
DT	delirium tremens
ECDEU	Early Clinical Drug Evaluation Unit
ECG	electrocardiogram
ECNP	European College of Neuropsychopharmacology
ECT	electroconvulsive therapy
EEG	electroencephalography
EPS	extrapyramidal signs
ES	experimental subjects
f	female
FDA	Food and Drug Administration
FGA	first generation antipsychotics
FMG	foreign medical graduate
fMRI	functional magnetic resonance imaging
FTE	full time equivalent
GS	government payment schedule
GA	Georgia
GABA	γ -amino-butyric acid
GAD	glutamic acid decarboxylase
GI	gastrointestinal
GP	general practitioner
GSK	Glaxo Smith Kline
Haldol	haloperidol
HD	Helsinki Declaration (Declaration of Helsinki)
HGH	human growth hormone
5-HIAA	5-hydroxy indole acetic acid
HMO	Health Maintenance Organization
HPA	hypothalamic pituitary adrenal axis
hs	hypochondriasis
5-HT	5-hydroxytryptamine (serotonin)

HVA	homovanillic acid
hy	hysteria
IBM	International Business Machines
ICD	International Classification of Diseases
IM	intramuscular
IND	Investigational New Drug
IRB	Investigational Review Board
IRCNP	International Reference Center Network in Neuropsychopharmacology
IRP	Intramural Research Program
ISI	Information Science Institute
IT	information technology
ITT	interpersonal therapy
IU	Indiana University
JAMA	Journal of the American Medical Association
JPET	Journal of Pharmacology and Experimental Therapeutics
KHA	Kefauver-Harris Amendment
KY	Kentucky
l	levo-
LA	Los Angeles
Lab	laboratory
LSD	lysergic acid diethylamide
LTP	long term potentiation
MAM	methazoxymethanol acetate
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
Mass General	Massachusetts General Hospital
Mass Mental	Massachusetts Mental Health Center
MDMA	methylenedioxyamphetamine (ecstasy)
MGH	Massachusetts General Hospital
MHPG	3-methoxy-4-hydroxy-phenylglycol
mGluR2/3	metabotropic glutamate receptor
MIT	Massachusetts Institute of Technology
MK	Merck
MMHC	Massachusetts Mental Health Center
MMPI	Minnesota Multiphasic Personality Inventory
MR	magnetic resonance
MRI	magnetic resonance imaging
MTPT	3-methyl-4-phenyl-tetrahydropyridine
Namende	memantine
NAMI	National Alliance for the Mentally Ill

NARI	noradrenaline reuptake inhibitor
NARSAD	National Association for Research in Schizophrenia and Affective Disorder
NaSSA	noradrenergic and selective serotonergic antidepressant
NCDU	New Clinical Drug Evaluation Unit
NDA	New Drug Application
NE	norepinephrine
NFL	National Football League
NHLBI	National Heart Lung and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institutes on Alcohol and Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINCDS	National Institute of Neurological and Communication Disorders and Stroke
NMDA	N-methyl-D-aspartate
NMR	nuclear magnetic resonance
NOS	not otherwise specified
NPI	neuropsychiatric hospital
NPY	neuropeptide Y
NSF	National Science Foundation
NYU	New York University
OB/GYN	obstetrics and gynecology
OCD	obsessive compulsive disorder
PACUC	Purdue Animal Care and Use Committee
PC	personal computer
PCHEM	physical chemistry
PCP	phencyclidine
PCP	primary care physician
pd	psychopathic deviant
PDR	Physicians Desk Reference
PEFI	psychoeducation family intervention
PET	positron emission tomography
PGY	post graduate year
PI	principal investigator
PNAS	Proceedings of the National Academy of Science
pt	psychasthenia
PTSD	post-traumatic stress disorder
R & D	research and development
RCT	randomized clinical trial
RDC	Research Diagnostic Criteria

REM	rapid eye movement (sleep)
RNA	ribonucleic acid
RO1	NIH Research Project Grant
RRC	research review committee
sc	schizoid
sc-pd	schizoid personality disorder
SGA	second generation antipsychotics
Sinequan	doxepin
SK&F	Smith, Kline&French
SMA5	serotonin modulating antidepressant
SNRI	serotonin-norepinephrine reuptake inhibitors
SRS	slow reading substances (lucotriens)
SSRI	selective serotonin reuptake inhibitors
Stan	Stanford
STAR	Scientific Technology and Resource
Stelazine	trifluoperazine
SUNY	State University of New York
TAT	Thematic Apperception Test
TD	tardive dyskinesia
THC	tetrahydrocannabinol
Thorazine	chlorpromazine
TR	translational research
TRH	thyroid releasing hormone
TSH	thyroid stimulating hormone
TSS	treatment strategies in schizophrenia
UC	University of California
UCI	University of California at Irvine
UCLA	University of California, Los Angeles
UCSD	University of California, San Diego
UCSF	University of California, San Francisco
UK	United Kingdom
UK	University of Kentucky
UNC	University of North Carolina
Undergrad	undergraduate
USD	University of California, San Diego
USDA	US Department of Agriculture
VA	Veteran's Administration
VAH	Veteran's Administration Hospital
VAHS	Veterans Administration Health Care System
VMA	vanillylmandelic acid
VOD	visiting overseas doctor

WHO World Health Organization
WPA World Psychiatric Association

INTRODUCTION & DRAMATIS PERSONAE

Carl Salzman

It is a pleasure to introduce this volume of oral ACNP history entitled "Diverse Topics". The interviewees, all distinguished members of the ACNP, are well known for their research, their teaching and for their leadership roles in administration of academic, industrial, or public health programs. The interviews are presented in alphabetical order; there are several interviewers, but the general format of the interview is shared among all.

Several characteristics of nearly all (if not all) of the ACNP interviews in this volume emerge with striking emphasis. Although this group has had fantastic academic, commercial and administrative success, not all came from a family with professional parents, and many did not attend the leading American universities for their education. Many of the members were not initially interested in science and did not pursue science during the university and graduate education. They were a wonderful group of interesting young people: musicians, English majors, non-psychiatric physicians, and the usual confused young people who were uncertain about their future paths. The few who were interested in science often came into the field through early laboratory experience, working in hospitals or health care facilities, and, in one case, learning a love for statistics as a means of discovering important patterns of illness to then be studied. Virtually all received their psychiatric training at the leading academic psychiatry residencies; a majority received part of their training at NIMH, and some remained at NIMH for part or all of their careers.

It is also interesting that of the 24 ACNP members who were interviewed for this volume, 7 (a little less than 1/3rd) had an initial interest or were studying psychoanalysis before they became interested in psychopharmacology. At least 3 continued to practice psychoanalysis as they began their scientific career, and 2 continued to be a practicing psychotherapist/analyst during their entire psychopharmacology career. On the other hand, several of the interviewees described their extreme displeasure and disillusion with psychoanalytic theory and treatment early in their career, amounting almost to repugnance!

Everyone interviewed stressed the importance of mentors early in their careers. Here are some of the names of important mentors who were explicitly mentioned by the interviewers (in alphabetical order): Axelrod, Baldessarini, Ban, Bliss, Brodie, Cole, Costa, Efron, Epstein, Freedman, Garver, Greenblatt, Heninger, Hippus, Judd, Kandel, Kety, Klerman, Klein, Kline, Lipton, Maas, May, Meltzer, Pope, Prange, Robins, Roth, Salzman, Schatzberg, Shader, Snyder and Zeller. Some of these mentors became close personal friends

and there are many amusing anecdotes of interactions between mentor and junior colleague. What is striking about these relationships, however, was the ability of the mentor to focus and more sharply define the interest of the junior colleague without directly intruding on their scientific autonomy. It appears that most of the mentors left the junior colleague alone to find their way into the science, with only occasional guidelines and encouragements. Not one of the interviewees complained that they functioned as “hired help” for the senior scientist’s pet projects, and all noted their inclusion in early publications and as grant recipients often as senior author or principal investigator.

As a group, these 24 interviewees were very successful in their careers. In academia, most of them were full professors, many with endowed chairs, and some were chairs of leading departments of psychiatry. A few became Deans and one is President of a large hospital. Leadership roles also extended to industry and to large public health systems. Everyone served on editorial boards of leading journals (several created their own journals), and in leadership roles in professional organizations. Most, if not all, received awards for excellence (some received numerous awards) for outstanding contributions to science and education. In all, a very, very impressive group of individuals!

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

Lastly, everyone interviewed was optimistic and enthusiastic about the future of psychopharmacology as a scientific and clinical endeavour growing out of the recent explosion of neurobiological discoveries as well as the emerging roles of genetics, and the use of new technologies to understand the physiology of mental functioning both normal and pathologic.

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

Dramatis Personae

The following pages introduce the *Dramatis Personae* of this volume in enough detail to give a framework of understanding their achievements.

Manfred Ackenheil began his medical career studying norepinephrine and serotonin metabolism. Dr. Ackenheil is extremely well known throughout Europe as well as in the United States and had a distinguished career pursuing research in psychoneuroimmunology and pharmacokinetics of psychotropic drugs. He participated in the European genome scan of schizophrenia and bipolar disorders, the genetics and biological markers of alcoholism, and of fibromyalgia. Ackenheil was Professor at the University of Munich and Head of the Department of Neurochemistry and Laboratory Medicine. In addition to being a Foreign Corresponding Fellow of the ACNP, he has been a leader in numerous European scientific and pharmacological organizations including the CIMP, the German Society of Biological Psychiatry, the European College of Psychopharmacology (president), the Section of Immunology in Psychiatry of the World's Psychiatric Association, and the International Foundation of Mental Health and Neurosciences (vice president). He was a member of the WPA Task Force on the Future of Psychiatry and Its Relation to Neuroscience, and of the Steering Committee of the European Science Foundation. He was also a corresponding member of the International Academy of Biomedical and Drug Research.

Charles M. Beasley received his undergraduate education at Yale University in New Haven, and his medical degree from the University of Kentucky College of Medicine. He was trained in psychiatry at Yale and at the University of Cincinnati. Virtually all through his career Dr. Beasley has been a distinguished psychiatrist with Eli Lilly Incorporated. He was part of the team that brought fluoxetine through its clinical trials and FDA approval process. He has remained involved in studying the therapeutic and side effect profile of the drug. Beasley was also engaged in studies of olanzapine in which he systematically investigated the relationship between the development of the metabolic syndrome and type II diabetes and the drug. Beasley has been a prolific author and contributor to the scientific literature. He is member of numerous medical and psychiatric societies, and the recipient of several research awards receiving the first ones while still in medical school and psychiatric residency.

Eva Ceskova received her MD and PhD from the Masaryk University of Brno in Czechoslovakia. She was trained in psychiatry at the same University. After graduation from medical school Dr. Ceskova joined the faculty of the Department of Psychiatry of the University; currently, she is Professor and Head of the Department. While she has been participating in clinical investigations with psychotropic drugs all through the years, her early research was focused on first-episode schizophrenia. In 1981 Ceskova spent six months with a WHO Scholarship in the USA (Nashville, Tennessee) for training in clinical psycho-pharmacological with Professor Thomas Ban at the Tennessee Neuropsychiatric Institute (Vanderbilt University). Ceskova has been active in

many scientific societies, serving as councillor in the CINP, president of the Czech Psychiatric Society, etc. She was the recipient in 1995 of the Professor Hanzlicek Award for her book on *Psychopharmaceuticals in Clinical Practice*, and in 2001 of the Paul Janssen Fund for the book she co-authored on *Clinical Nutrition in Psychiatry*.

Dennis S. Charney received his undergraduate degree from Rutgers College and his MD from Pennsylvania State University. His psychiatric training was at Yale. After completion of his training Dr. Charney joined the faculty of the Department of Psychiatry; he became the Chief of the Psychiatric Service of the West Haven VAH and Co-director of the VA's Schizophrenia Biological Research Center. Charney is known for his pioneering work in the neurobiology of anxiety, panic disorders and post-traumatic stress disorder (PTSD). He rose to the rank of Professor of Psychiatry at Yale. From Yale, Charney moved to the NIMH, and then became Dean of the Mount Sinai School of Medicine, and Professor in the Department of Psychiatry. Charney received numerous distinctions for his outstanding research in psychiatry including the Daniel Efron Research Award of the ACNP. He is a prolific author, and co-editor (with Eric Nestler) of the seminal volume, *Neurobiology of Mental Disorders*.

Joseph T. Coyle received his medical degree from Johns Hopkins University in Baltimore, after graduating with honors from the college of Holy Cross in Worcester, Massachusetts. He was a psychiatric resident at Hopkins, and then served three years as a Research Associate in the NIH laboratory of Clinical Science under Julius Axelrod. Dr. Coyle is known for his pioneering elucidation of the role of acetylcholine in cognition and cognitive disorders as well as for his work on the role of glutamate in schizophrenia. Coyle's professional career rocketed from Hopkins to the Harvard Medical School where he became the first Chair of the Consolidated Department of Psychiatry and Eben S. Draper Professor of Psychiatry and Neuroscience. He oversaw the expansion and development of collaborative research, teaching and clinical efforts at this very large and geographically widespread department while continuing his own basic neuroscience research. Coyle won an extraordinary number of awards testifying to his outstanding leadership role in psychiatric and psychopharmacological research. Included among these honors are: the A.E. Bennett Clinical Science Research Award, and the Gold Medal of the Society of Biological Psychiatry, the John Jacob Able Award of the American Society of Pharmacology and Experimental Therapeutics, the Daniel Efron Research Award from the ACNP, and the Foundations Prize for Research in Psychiatry from the APA. Coyle is an elected fellow of the American Academy of Arts and Sciences. He served as the editor-in-chief of the Harvard Review of Psychiatry, and is currently editor-in-chief of the *Archives of General Psychiatry* of the American Medical Association. .

Kenneth L. Davis received his undergraduate degree from Yale in New Haven, and his medical degree from the Mount Sinai School of Medicine in New York. His research focused on the neurobiology of dementia, as well as on the neurobiology of schizophrenia. As a result of his extraordinary contributions to both of these areas, Dr. Davis is the recipient of numerous honors including the A.E. Bennett Clinical Science Research Award and the Gold Medal of the Society of Biological Psychiatry, the Joel Elkes and the Daniel Efron Research Awards of the ACNP, and APAs Award for Research in Psychiatry. In addition to his outstanding research career and presidency of the ACNP, Davis rose from Professor and Chair of the Department of Psychiatry and Pharmacology of the Mount Sinai School of Medicine to become the Dean of the Mount Sinai School of Medicine. Currently, he is President and Chief Executive Officer of the Mount Sinai Medical Center.

Michael H. Ebert obtained his undergraduate degree from Williams College and his medical degree from Case Western Reserve University in Cleveland. Dr. Ebert was a resident in psychiatry at the Massachusetts Mental Health Center in Boston and began his research career at that institution working with Richard Shader and Carl Salzman. He then went to the NIMH where he was Chief of the Unit on Clinical Pharmacology first, then Chief of the Section on Experimental Therapeutics of the Laboratory of Clinical Science, and ultimately Acting Clinical Director of the Intramural Research Program. From this position he moved to become Chairman of the Department of Psychiatry and Professor of Psychiatry and Pharmacology of Vanderbilt University where he remained until becoming Chief of Staff at the West Haven VA Hospital. Ebert has achieved distinction as a researcher focused primarily on monoaminergic neurotransmission in psychiatric disorders, but also has achieved distinction as an educator in psychiatry, a builder of clinical treatment facilities and programs and ultimately as a national leader in health care administration.

Ellen Frank graduated from Vassar College in Poughkeepsie, New York, and then received a Master's degree in English and a Master's degree in Psychology before receiving her PhD in Psychology from the University of Pittsburg. Dr. Frank's research has focused primarily on the treatment of affective disorders and she is known for her seminal studies on the importance of maintenance treatment for major depressive disorder. She has received numerous honours for her research including a merit award from the NIMH, and a national lifetime award from the National Depressive and Manic Depressive Association. She is also a recipient of the National Media Award of the American Psychological Association.

Peter Gaszner received his MD from the University of Debrecen, Hungary, in 1963, and earned diplomas in neurology, psychiatry and clinical pharmacology in 1957, 1970 and 1980 respectively. He was trained in psychiatry in

the Department of Psychiatry at the University of Pecs. Dr. Gaszner was involved in research with atropine coma therapy and in human pharmacological studies on the peripheral effects of neuroleptics and antidepressants, using psychophysiological indicators. He also developed (in collaboration with Thomas Ban) a composite diagnostic evaluation for hyperthymic disorders, suitable for the study of drugs used in these disorders. Gaszner was Director of Psychopharmacology at the National Institute of Neurology and Psychiatry of Hungary and Professor of Psychiatry at Semmelweis University. He served as Vice President of the European College of Neuropsychopharmacology and is Founding President of the Hungarian Psychopharmacology Society. Gaszner is also founding editor-in-chief of *Neuropsychopharmacologia Hungarica*, the journal of the society. He is currently one of the editors of the *Journal of Neurotransmission*.

Ira D. Glick attended Dickinson College in Carlyle, Pennsylvania, and the New York Medical College receiving his psychiatric training at Hillside Hospital and at Mount Zion Hospital in San Francisco. Dr. Glick studied psychoanalysis for one year. His early research was based on the family dynamics of major mental illness and he designed psychiatric treatment programs based on his research findings. He also received several awards for this family oriented research on psychosocial aspects of schizophrenia. Glick's psychopharmacology research has been primarily focused on the treatment of schizophrenia. He has been the Associate Medical Director of the Payne-Whitney Clinic and the New York Hospital Medical Center after first serving as a Professor of Psychiatry at UCSF. He subsequently returned to California as a Professor of Psychiatry at Stanford University and Chief of Psychiatry at the Palo Alto VAH. Glick has an international reputation, lecturing throughout the world on uses of psychiatric drugs. He has participated in numerous multi-site trials, and has collaborated on seminal meta-analyses of new antipsychotic medications. He has also served as a Consultant to the Director of the National Institute of Mental Health helping to design a broad-based psychopharmacology research programs. He is especially well known for his significant contributions to psychiatric education programs especially through the ACNP, and has won numerous teaching awards including the Vestermark Award from the APA.

George R. Heninger received his undergraduate and medical degree from the University of Utah. He was a psychiatric resident at the Massachusetts Mental Health Center in Boston, where he was introduced to psychiatric research by Milton Greenblatt, Gerald Klerman, and Richard Shader. Dr. Heninger's research has focused on basic mechanisms of mood disturbance and anxiety disorders with special attention to the role of serotonin and serotonin precursors. He serves as Director of Clinical and Molecular Biology at

Yale. Heninger was awarded the first prize of the Anna Monika Foundation for his research in depression.

Fritz A. Henn received his bachelor's degree from Wesleyan University, in Middletown, Connecticut, his PhD from Johns Hopkins University, and his MD from the University of Virginia. He began his psychiatric training at the University of Iowa and within a decade he became Professor and Chairman of the Department of Psychiatry and Behavioral Medicine at the State University of New York at Stony Brook. Subsequently he became Director of the Institute of Mental Health Research SUNY at Stony Brook Health Science Center. Currently he serves as Professor of Psychiatry in the faculty of clinical medicine of the University of Heidelberg at Mannheim in Germany. He is also Director of the Department of Psychiatry and of the Central Institute of Mental Health in Mannheim. Dr. Henn's research has focused on neurobiological mechanisms of major mental disorders at the molecular level. He has been active in European and American scientific societies, serving with distinction in the Association of European Psychiatrists, the American College of Psychiatrists, the ACNP, Psychiatric Research Society (President), and the European College of Neuropsychopharmacology. He has also served on numerous federal advisory committees and has been a member of the Institute of Medicine of the National Academy of Science.

Lewis L. Judd received his bachelor's degree from the University of Utah and his MD from UCLA. Dr. Judd's early work was at the interface between psychiatry and medicine. He joined the Department of Psychiatry of University of California, San Diego (USD), and became first Co-Chairman of the Department, of Psychiatry, then President, and ultimately, Chairman of the Department. He was also appointed a Distinguished Professor. For two years Judd served as the Director of NIMH where he fostered the development of large-scale collaborative research programs. He is one of the most noted leaders of American psychiatry and psychopharmacology. Judd is the recipient of various awards, including the Distinguished Service Award of NAMI, and the Awards of Distinction of the Linda Poln Foundation, and of the National Leadership in Child and Adolescent Mental Disorders. He was elected a member of the Institute of Medicine of the National Academy of Sciences (USA).

Joel E. Kleinman received a bachelor's degree in biochemistry, an MD, and a PhD in Pharmacology from the University of Chicago. He was a psychiatry resident at the Massachusetts Mental Health Center where he trained under Richard Shader and Carl Salzman, and then went to the NIMH. During his early years at NIMH, he was also a neurology resident at George Washington University. Dr. Kleinman's entire professional career has been at NIMH. Initially he served as a Clinical Associate in a laboratory of clinical psychopharmacology; he then became Chief of the Clinical Brain Study Section and at

present is Deputy Chief of the Clinical Brain Disorders Branch and Chief of the Neuropathology Section. Kleinman also serves as an Associate Clinical Professor at George Washington University, Department of Psychiatry and Neurology. He is best known for his neuropathological studies of the brains of patients with schizophrenia. He is the recipient of the A.E. Bennett Clinical Science Research Award of the Society of Biological Psychiatry, as well as the United States Public Health Service Outstanding Service Medal for his research leadership.

Stephen H. Koslow received his bachelor's degree from Columbia University in New York, and his PhD from the Department of Pharmacology at the University of Chicago. He worked at the Karolinska Institute in Stockholm (Sweden), and was a Fellow at NIMH in the Laboratory of Preclinical Pharmacology. Dr. Koslow rose from Fellow to the position of Chief of the Biological Research Section in the Division of Extramural Research Programs, and became first, Chief, of the Neuroscience Research Branch, then, Deputy Director of the Division of Basic Brain and Behavioral Research, and, finally, Director, of the Division of Neuro- and Behavioral Sciences. In all these positions he fostered collaborative research, created behavioral science task forces promoting the continued development of research grants. Koslow coordinated biological and clinical research efforts at a national level, and initiated NIMH's psychotherapeutic medication development programs, scientific technology and resource (STAR) programs, and the human genome project. His background in research served as the basis for his future career as an administrative visionary helping to create and foster major collaborative research efforts in neuroscience and psychopharmacology.

Paul Leber received his undergraduate degree from Hamilton College, Collins, New York, and his MD from NYU, achieving honours at both institutions. He received post-graduate training in internal medicine and in pathology before becoming interested in psychiatry. Dr. Leber is Board Certified in pathology, psychiatry and neurology. After positions in pathology and psychiatry at SUNY Buffalo, Harvard Medical School, and NYU, Leber joined the US Food and Drug Administration, where he rose to become Director of the Division of Neuropharmacological Drug Products. He is known as a careful interpreter of data submitted to the FDA; concerned for the protection of patients who might take new medications.

Roger Maickel received his undergraduate degree in Chemistry from Manhattan College, New York, and Masters and PhD degrees in Chemistry from Georgetown University in Washington, DC. Dr. Maickel started his career as a research biochemist at the National Heart Institute of NIH where he rose to become the Head of the Section of Biochemistry in the Laboratory of Clinical Pharmacology. From NIH, he moved to Indiana University in

Bloomington, where he rose to Professor of Pharmacology and Head of the Section on Pharmacology in the Medical Sciences Program. From IU he moved to Purdue University, in West Lafayette, Indiana to become Head and Professor of Pharmacology and Toxicology at the School of Pharmacy and Pharmacology Sciences at Purdue University. Maickel's work in basic pharmacology and psychopharmacology has brought him numerous awards including a Life Sciences Award from NASA, as well as a Research Development Award from NIMH. His international prestige led him to memberships not only in the ACNP but also in the American Society for Pharmacology and Experimental Therapeutics, the CINP, and in the International Brain Research Organization, and the International Society for Psychoneuroendocrinology. .

Arnold J. Mandell received his undergraduate education at Stanford University, and his MD at Tulane University in New Orleans. He served his psychiatric residency in the Neuropsychiatric Institute and the Brain Research Institute of UCLA. After his residency he did graduate work in Organic Chemistry, Biochemistry and Neurochemistry at UCLA. Mandell was Founding Chairman of the Department of Psychiatry, UCSD, La Jolla from 1969 to 1977, and Director of the UCSD Laboratory of Biological Dynamics and Theoretical Medicine from 1969 to 1990. He has received numerous awards, including the Foundation Prize of the American Psychiatric Association, and the A.E. Bennett Award of the Society of Biological Psychiatry. Currently, he is Professor Emeritus UCSD and Vice President for Research, Cielo Institute in Asheville, North Carolina.

Aleksander A. Math received his MD from the University of Zagreb, Yugoslavia, and his PhD from the Karolinska Institute in Stockholm. He was trained in psychiatry at Boston University, where he subsequently became an Associate Professor of Psychiatry and Pharmacology and the Director of the Laboratory of Biogenic Amines and Allergy. From Boston, he moved to New York to become Associate Professor of Psychiatry and Director of the Biochemistry Laboratory at the Mount Sinai School of Medicine, before returning to Stockholm to become Professor of Psychiatry and Director of Psychiatric Education at the Karolinska Institute. Over the years Dr. Mathé extended his research from neuropeptides to the study of genomics and proteomics of depression. He is the recipient of numerous awards from the World Congress of Psychiatry, the Scandinavian Society of Psychopharmacology, the Scandinavian College of Neuropsychopharmacology, the Swedish Psychiatric Association, and the Swedish Medical Society.

Charles B. Nemeroff received his undergraduate education at the City College of New York, his Master's of Science at Northeastern University in Boston, and his PhD and MD at the University of North Carolina. He served his psychiatric residency in the Department of Psychiatry of the University of North Carolina. Dr. Nemeroff's interests in psychiatry began while working as a

research assistant at McLean hospital and the Beth Israel hospitals in Boston before obtaining his graduate degrees. Following his residency, he became Assistant Professor in the Department of Pharmacology at Duke University, in Durham, North Carolina, and rose first to become Director of the Laboratory of Psychoneuroendocrinology, and subsequently, Chief of the Division of Biological Psychiatry in the Department of Psychiatry. From Durham, Nemeroff moved to Atlanta to become Professor and Chairman of the Department of Psychiatry and Behavioral Sciences at Emory University. Nemeroff is one of the best known psychiatrists and psychiatric researchers in the United States. His primary areas of research include psychoneuroendocrinology, the biology of affective disorders, and the neurobiological consequences of trauma. His papers, edited books, as well as numerous chapters in textbooks are extensively used in the teaching of psychopharmacology. Nemeroff is the recipient of numerous awards, including, the A.E. Bennett Scientific Research Award, and the Gold Medal of the Society of Biological Psychiatry, the Daniel Efron Research Award of the ACNP, the Kurt Richter Award of the International Society of Psychoneuroendocrinology, the Selo Prize for Research in Mood Disorders of the National Alliance for Research in Schizophrenia and Affective Disorders, etc.

Carl Salzman received his undergraduate education at Union College in Schenectady, New York and his MD from the State University of New York Upstate Medical Center in Syracuse. His psychiatric training was at the Massachusetts Mental Health Center (MMHC) where he returned as a faculty member after two years at NIMH working with Jonathan Cole and Jerome Levine. At the Massachusetts Mental Health Center, Dr. Salzman began his psychiatric research career under Richard Shader and Gerald Klerman in the psychopharmacology program which he later directed. . Salzman is best known for his research in benzodiazepines and geriatric psychopharmacology. He was once fancifully called “The Father of Geriatric Psychopharmacology”. He is also noted for his contributions to psychopharmacology education. Salzman is Professor in the Department of Psychiatry at Harvard Medical School. He is the recipient of several awards including the Heinz E. Lehmann Research Award from the State of New York Office of Mental Health, and the Vestermark Award, shared with Richard Shader, from the APA. He is also the recipient of numerous national awards for teaching excellence

Richard I. Shader received his undergraduate training at Harvard College in Boston, and his MD from NYU. He trained in psychiatry at the Massachusetts Mental Health Center and graduated from the Boston Psychoanalytic Institute. Dr. Shader’s research career began under the direction of Milton Greenblat and Gerald Klerman at the MMHC where he assumed the Directorship of the Psychopharmacology Program and created a vibrant research program

in benzodiazepines, clinical pharmacokinetics, and geriatric psychopharmacology. Shader then became Professor and Chairman of the Department of Psychiatry at Tuft's University Medical School in Medford, Massachusetts, and ultimately Professor and Chairman of the Department of Pharmacology and Experimental Therapeutics at the University. Shader gained international reputation for excellence in research and teaching in psychopharmacology. He has also a reputation of being an outstanding psychotherapeutic and psychoanalytic clinician. Shader received numerous awards including a Merit Award from the NIMH, the Vestermark Award (shared) from the APA, and a fellowship from the Institute of Advanced Study in the Behavioral Sciences at Stanford University.

Stephen M. Stahl received his undergraduate training and MD at Northwestern University in Evanston, Illinois and his PhD in neuropharmacology from the University of Chicago. Dr. Stahl's training in neurology was at UCSF, and in psychiatry at Stanford. In addition to his own research, which focused on movement disorders and neuropharmacology of monoamines, Stahl is widely noted for his outstanding abilities as a psychopharmacology educator. His books, lectures, teachings are used throughout the world and have become the mainstay of many training programs. Stahl has been the recipient of the A.E. Bennett Award in Basic Research of the Society of Biological Psychiatry, as well as the Gene Milton Shy Award, and the G.D. Searle Award. He is a member of the British Association of Psychopharmacology and the British Pharmacology Society, the International Society of Neurochemistry, and the Royal Society for Medicine (UK).

Gary D. Tollefson received his bachelor's degree, MD, and PhD from the University of Minnesota. Early in his career he joined the Eli Lilly Company where he served first as the Executive Director of the Research Laboratories, and then as Vice President, and finally, as President of the Neuroscience Products Division. He was also appointed a distinguished Eli Lilly scholar. Tollefson is recognized as one of the leading forces in the productive collaboration between industry and academic research for the development of new psychotherapeutic medications, including fluoxetine and olanzapine. He was also instrumental in expanding the research department of Eli Lilly through the recruitment of outstanding psychopharmacology leaders and members of the ACNP.

INTERVIEWEES & INTERVIEWERS

MANFRED ACKENHEIL

Interviewer, Andrea Tone
San Juan, Puerto Rico, December 15, 2004

AT: My name is Dr. Andrea Tone and we're at the 2004 Annual Meeting of the ACNP in Puerto Rico, and this morning, it is my pleasure to interview Dr. Manfred Ackenheil.* Thank you for agreeing to the interview.

MA: Thank you, Andrea.

AT: We want to walk you through your personal history and your professional history, learn more about your upbringing, the contributions you've made, your reflections, looking back. So, why don't you start from the very beginning? Tell us where you were born, when you were born, your upbringing.

MA: OK. I was born in Frankfurt, Germany. I grew up in Baden-Baden, which is on the border of France, nearby Strasbourg. Therefore, I speak relatively good French, Italian and Spanish that later on was important for my career. I went to school in Baden-Baden and continued with my studies in Freiburg, Heidelberg, and Munich. Originally my intention was to study architecture and not medicine or pharmacy, but my parents convinced me to study first pharmacy. My father was the CEO of a company that was part of a chain of pharmacies. But pharmacy was boring for me.

AT: Why was it boring?

MA: Selling of drugs was not for me. So, I went to study medicine. But because of my background in pharmacy I was very good in chemistry, much better than the average student in medicine. So, I wrote my thesis in an area of biochemistry at the Max Planck Institute of Psychiatry in Munich. There, I met, for the first time, Norbert Matussek. This was in the 1960s. Matussek was a very impressive man; he was a pioneer. He worked in the USA in the laboratory of Bernard Brodie, together with Arvid Carlsson, Erminio Costa and many others. It seems that at the time they were not only doing research and working in the laboratory but also discussed life, suffering, and whatever, in the evenings. It was the same in Germany in those years.

AT: Do you think that approach has been lost today?

MA: I believe it's lost. They had much more personal connections with each other than we have today. We met with Norbert Matussek very often on weekends. And I remember from our conversations that he was convinced that we are close to an understanding of depression and schizophrenia. Of course today everything in that area of research is much more complex

* Manfred Ackenheil was born in Frankfurt, Germany in 1939. Ackenheil died in 2006.

than we thought in the late 60th. But still, our ideas today are similar to the ones we had at the time. For example, we studied the function of synaptic vesicles in which monoamine neurotransmitters are stored. We had the idea that they serve as a buffer that is altered in manic-depressive illness. We also worked with the stress model of psychiatric disorders that implies that some psychiatric disorders, e.g., depression are the result of excessive stress that the subject could not cope with. So, we developed the swimming survival test in rats and found that antidepressants could reverse the stress-induced changes in the animals. We didn't publish our findings but they were given in my dissertation that dealt with the effects of antidepressants on the swimming survival test.

AT: That's great. What was the impact?

MA: It was to become used in the screening for antidepressants, so it had had an impact on the development of drugs for the treatment of depression. Arvid Carlsson gave reserpine and another compound, that I don't know exactly the name of that made rats or mice cataleptic, in a way depressed. But he noted that if he treated the animals with antidepressants before giving reserpine, instead of becoming cataleptic the animals became hyperactive. We usually used monkeys and rats in our animal experiments, and we intended to replicate Carlsson's findings in rats. But, and this is a funny story, while we were trying to replicate his findings the animals disappeared.

AT: At least, it wasn't the monkeys.

MA: They were under the table. Nowadays, everything must be well organized; the animals are kept in cages and so on. But this was not the case in those days.

AT: Did the rats become aggressive when they were hyperactive?

MA: Maybe they didn't like the way they were being treated by us.

AT: That's funny.

MA: Okay. At the end of the 1960s I passed my examination in medicine. By then I was about 26 years old and published several papers. My intention was to go to the United States or Canada. I would have preferred to go to Canada because of the language. At the time, I spoke much better French than English. So, I wanted to go to Canada to work with Heinz Lehmann, who was a pioneer in psychopharmacology. I was trying to go there for two years but by the time I got my grant that would allow me to go I was offered a position in Germany. It was a very good position in a department of psychiatry. So I thought it might be better for me to stay home.

AT: Why do you think you were favored for the position you got in Germany? Why did they choose you?

MA: I was chosen because I had already some publications and I also knew how to use assays for measuring catecholamines, such as norepinephrine and dopamine, as well as serotonin. That was unusual for a medical doctor. So, they could ask me to run a laboratory.

AT: How prevalent was biological psychiatry in Germany at the time?

MA: It was more prevalent than in the United States, because in the United States, at the time, psychoanalysis prevailed. Of course, psychoanalysis was also very popular in Germany in those years, but it was less popular than in the United States. In the psychiatry departments of the universities in Germany there were psychiatrists, not psychoanalysts as in the United States. But to continue with my story I went to work in a small town in Germany to run a laboratory in the Department of Psychiatry there, and I didn't like it. So, I trained somebody for the job and went back to Munich after a year. You must know that in Germany, Munich is the best city to live in. In so far as quality of life is concerned it is better than Berlin. It's a city of culture. And, at the same time you can go to ski in the mountains in half an hour. And we have also many lakes in Munich. I lived in Berlin before. I actually started my studies at the time when there was a student revolution there and we fought against the professors.

AT: What did you do after your return to Munich? Were you trained in psychiatry in Munich or in Berlin?

MA: I worked in internal medicine. I'm not a psychiatrist. . You can do the same kind of research in internal medicine as in psychiatry. The neurotransmitters play just as much a role in hypertension than in mental illness. So, I spent several years in internal medicine. I was involved in research with β -blockers.

AT: That's very interesting.

MA: I was working in internal medicine for 12 years before moving to psychiatry. What actually happened was that Hanns Hippus moved from Berlin to Munich to become Head of the Department of Psychiatry at the University, and convinced Norbert Matussek, who was working at the time in the Max Planck Institute of Psychiatry in Munich, to join him.

AT: How did he do that?

MA: Norbert Matussek moved from the Max Planck Institute to Hippus' Department of Psychiatry at the Ludwig Maximilian University of Munich. Hippus was an exceptionally good manager and very much interested in biological psychiatry. So, he was able to set up a big and well-equipped laboratory. Both Hippus, whom I met first while he was professor in Berlin, and Matussek, knew that I set up before a clinical chemistry laboratory in a department of psychiatry. So, they invited me to join the department and work with Norbert Matussek. Hippus was skeptical in inviting

me first because he knew that I was one of those students who had long hair and fought against him and the other professors in Berlin. But, as time passed we became very good friends. And, so, we established with Norbert Matussek in Hippus' Department of Psychiatry a research unit that was to become very soon the most important research unit in psychiatry in Germany, or possibly even in Europe, because we had the best facilities for doing biochemical research. Of course, the Max Planck Institute had also excellent facilities but in those years the director of the Institute was not interested in the kind of research we were doing. There was a very pleasant working environment in the Department of Psychiatry at the University of Munich. I had a lot of fun with Norbert Matussek; and not only doing the work in the laboratory but also otherwise. For instance, we organized a conference in the southern part of France, and, combined it with a tennis tournament or skiing. In sports I was much better than Norbert Matussek, although he liked sports, as well. Since Hanns Hippus came from the Northern part of Germany, he liked to go to the mountains in Bavaria. I always liked to ski, and of course, if you are coming from the South of Germany, you are a much better skier than those from the other parts of the country. I also played very good tennis. So, we organized many meetings that were combined with sports. And, we also went to the October Fest in Munich together. Norbert Matussek was a very social person. He knew many people and invited them to Munich. And, in return we were invited to many places. So, it was a very good atmosphere in the laboratory, and, at the same time, we were successful in our research. Of course, our interest in stress and depression continued, but since my primary interest was in the psychopharmacology of schizophrenia, we have done research in both areas. Norbert Matussek was more specialized in depression than I was and we worked together. At meetings I presented mostly on schizophrenia and he presented mostly on depression, but, of course, I was involved in both. We worked on the catecholamine hypothesis of depression and I considered norepinephrine, the key neurotransmitter in depression. When the serotonin hypothesis was proposed there were two competing hypotheses. I remember that at the first World Congress of the Societies in Biological Psychiatry in Argentina, there was a proponent of the serotonin hypothesis of depression and we participated in the same session. So, if he said, it is serotonin, I immediately retorted, no, it is norepinephrine.

AT: The two of you couldn't get along with your different neurotransmitters.

MA: Matussek and Ruether published the proposal in 1967 that norepinephrine and serotonin together are both involved in the pathophysiology of depression. We had the methodology to measure also serotonin,

because it was the same as the methodology to measure norepinephrine. And we measured a metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and a metabolite of dopamine, homovanillic acid (HVA). We measured the metabolites of all three neurotransmitters in the same sample from the cerebrospinal fluid. This was at the time when clozapine, the first atypical antipsychotic drug was introduced. I was interested in the mechanism of action of clozapine. I was really interested in the mechanism of action of all new antipsychotic drugs. One of the other new antipsychotic drugs marketed in those days was sulpiride, structurally a benzamide. I treated rats with clozapine, sulpiride, haloperidol, and other antipsychotics, and after treating them with one or another of these drugs I removed their brains and measured the metabolites of the three-monoamine neurotransmitters in the different areas of the brain. And, of course, clozapine did not produce extrapyramidal motor disturbances. Sometimes, I had fights with co-workers of Paul Janssen because they insisted at the time that one needs extrapyramidal motor disturbances to get antipsychotic effects. One of the friends of Paul Janssen was the German psychiatrist Haase, who was to become known for his handwriting test in the detection of the neuroleptic threshold of antipsychotic drugs. Haase, in English, is an animal that you can eat.

AT: Is it part of the poultry family? Rabbit perhaps?

MA: Yes, it's rabbit, of course. When I presented a paper on clozapine in conferences and Haase was present he did not miss a chance of telling me that this drug will not be effective in schizophrenia. Later on, clozapine was given the brand name, Leponex, which means without rabbit, without Haase.

AT: Is that why it got named that way?

MA: I don't think so. It was by chance.

AT: Are you sure? It sounds like you had an exciting time in research.

MA: Yes, it was an exciting time. In Germany you have to write your habilitation, before becoming a professor. It's just a little bit more than writing a PhD thesis. You have to write a thesis as a student, and, later on you have to write a thesis to become appointed a professor. And I had done my thesis on the mechanism of action of clozapine. In my thesis I advanced the theory that in addition to the nigrostriatal dopamine system, clozapine also affects the mesolimbic dopamine system, and it has adrenergic effects as well. Later on it was also recognized that it modulates the serotonin system. I presented the importance of the serotonin system in the mode of action of clozapine for the first time at a meeting in Padova, Italy that was organized by the so-called, "serotonin club".

The meeting took place long time before clozapine was introduced in the United States.

AT: Do you remember what year you attended the meeting in Padova?

MA: It was sometime in the 1970s, probably in 1975. We also continued our research on stress and psychosis. We developed methods for producing stress by exposing patients to stressful situations and measured their physiological reactions and blood levels of norepinephrine, cortisol and so on. The stress was produced by loud noise, social situations, and frightening movies, like Hitchcock's Psycho.

AT: Psycho?

MA: Psycho, yes.

AT: That'll cause anyone to have stress.

MA: It was in the 1980s when someone re-invented panic disorder in psychiatry that was known before in internal medicine as cardiac neurosis.

AT: Da Costa's syndrome?

MA: No, it was known as agoraphobia before. Panic disorder in psychiatry was introduced together with alprazolam.

AT: Alprazolam's brand name here is Xanax.

MA: We took part of the multi-center, multi-national study that established the effectiveness of alprazolam in panic disorder. I was the principal investigator of it at our site because the person in our department who conducted the investigations did not speak English. Since I was the one who spoke English I had to go to the investigators meeting to the United States. It was my first trip to the States. In the beginning, we could not find enough patients. It was a different situation from the United States where the investigators advertised for patients in newspapers. In Europe, we could not advertise in a journal for patients. However, we were involved in this study.

AT: Out of curiosity, how were you able to recruit patients to your study? How did you get them?

MA: We had to find them at outpatient clinics. The system is different in Germany from the USA. At the university departments we have many beds for inpatients. In Munich, we have 200 beds and if a patient is feeling ill, he comes to the university hospital and is admitted. But patients with panic disorder don't need to be admitted to hospital. So we had to find them at the outpatient clinics. And, then, the press attacked us for doing experiments that were not ethical. And we were attacked not only about the investigations in panic disorder with alprazolam, but also about our experiments with stress in which we exposed people to heat by putting them in a bath, and increased the temperature of the water to 42 °C.

- AT: Yikes! You just put them in hot water, right?
- MA: Yes, we did. We had to stop those experiments. We also induced stress as I told you before by showing movies to the patients, the kind of movies people can see on television.
- AT: And the press portrayed you as Sir Frankenstein. Did they make any analogies to experiments during World War II? This is something that Herman van Praag experienced as a researcher. Did they do that to you?
- MA: Yes, of course. We had to stop those experiments. Then, we were looking for a method that would provide information on the activities of neurotransmitters in the brain. This is how we got involved in endocrinology, to the stimulation of growth hormone with clonidine. Clonidine is an α_2 agonist that stimulates growth hormone release. And we found that in depressed patients the growth hormone response to clonidine is much less than in normal subjects. So, this was a methodology that allowed us to look into the brain. It was a similar method to the stimulation of dopamine by apomorphine that was used in schizophrenia. Recently, we are conducting research in psychoimmunology. Neurotransmitters are modulating the activity of the immune system. It was proposed that the immune system might play a role in schizophrenia.
- AT: Yes, I just heard about that at this meeting. That's very interesting.
- MA: We started our activities in this area of research 10 or 15 years ago.
- AT: Let me ask you a couple of questions. How do you see psychiatry in Germany? Did it change since the time you became involved in psychiatry?
- MA: It's now much more a part medicine. As I told you I was trained in internal medicine and not in psychiatry. Later on I got specialized in clinical pharmacology. This is now a specialty like psychiatry and to be a clinical pharmacologist one must be trained in internal medicine. One of my current interests is cardiovascular disease that occurs simultaneously with depression. The mortality of cardiovascular disease if combined with depression is much higher than without depression. Another area of research I'm interested in these days is the relationship between pain and depression. One of the pain disorders is called fibromyalgia. It is a disease that produces widespread pain. I started my research in fibromyalgia about eight years ago in collaboration with a neurologist and we hypothesized that in fibromyalgia the serotonin system is involved. We tested the serotonin hypothesis of fibromyalgia and found serotonin levels low. We also found a close association between fibromyalgia and depression. Most patients with fibromyalgia are treated by neurologists and not by psychiatrists, but they are using antidepressants in the treatment of these patients together with psychotherapy as if they were psychiatrists. Twenty or thirty years ago there was a tendency in medicine

to become more and more specialized. But, nowadays, since we have biological correlates the separation between psychiatry and neurology is no longer necessary.

AT: Right.

MA: In some countries, Alzheimer patients are treated in the department of neurology, whereas in other countries they are treated in departments of psychiatry.

AT: That's very interesting. You were instrumental in introducing the teaching of psychopharmacology in the medical curriculum in Germany. Is there anything you would like to comment relevant to teaching pharmacotherapy with psychotropic drugs?

MA: I'm a clinical pharmacologist and this is reflected in my teaching of psychopharmacology. I'm attending many conferences in psychiatry and in these conferences I hear that the doctors are reporting usually on monotherapy with drugs whereas in reality most of the patients, at least in Europe, and I believe it's the same in the United States, are treated on the basis of trial and error with about three different drugs simultaneously. It's unlikely that a schizophrenic patient is treated only with an antipsychotic, or a depressed patient is treated only with an antidepressant, or a bipolar patient treated only with a mood stabilizer. Very often, the patients are treated simultaneously with an antipsychotic, an antidepressant and a mood stabilizer. This is more the rule than the exception. Maybe, it's necessary to treat patients with several different medications simultaneously. But, then, we have to understand the realities of clinical pharmacology, namely that if you have 10 patients and you treat all of them with 10 mg of the same drug you may have ten different blood levels, a different level of the drug in each patient. Many factors need to be considered when prescribing a drug. Women are usually much smaller than men, and still they are usually treated with the same doses as man. There are pharmacokinetic differences between people and there are also genetic differences. We need to tailor pharmacological treatment to the need of individual patients. My primary interest today is tailoring medication to individual patients.

AT: Let me ask you two more questions, and then you can add on anything that you think I've forgotten or you would like to share. Where do you see psychopharmacology is heading?

MA: Since the development of proteomics or genomics we understand that the serotonin and norepinephrine systems are not independent or separate systems from each other. At the beginning of this interview I talked to you about the role of synaptic vesicles in which neurotransmitters are stored in the mode of action of psychotropic drugs. Then we learned

about the role of receptors, membranes, and all kinds of other structures. Today we recognize hundreds of proteins that are different genetically. We are moving in the direction to identify genes responsible for different kinds of mental illness, but in my opinion we will not find a gene that is responsible for schizophrenia or depression. There are probably at least several hundred genes that are responsible for some neurological disorders, e.g., Huntington's disease. It is also problematic to say we have the gene for something because each gene shows great variations.

AT: This is an important point, but how come we don't hear it being articulated here? There's a lot of interest in finding the gene for one or another disease.

MA: Geneticists, of course are trying to find the gene, even if they know that each gene shows great variations. But, then there are problems also with diagnostic classifications.

AT: I'd like to hear more of your thoughts on that.

MA: Insofar as I see it, it hasn't been an advantage in all respects, that everybody speaks the same language of DSM-III, DSM-IV or ICD-10. Clinical experience using psychotropic drugs in treatment shows that these classification systems do not really describe the disorders. The same applies to biological findings. High cortisol levels are not specific for depression. It may occur in other disorders, as well. It actually occurs in schizophrenia as well. And it also occurs in Alzheimer's disease. I'm very, very skeptical about the concept of co-morbidity. We may have a disturbance in the serotonin system, which leads to different symptoms. Serotonin is modulating different behaviors; it is involved in pain, eating, aggression, sexuality and whatever. There is a funny book by Donatella Marazziti, an Italian psychiatrist. It is on the *Biology of Love*. She suggests that falling in love is like obsessive-compulsive disorder.

AT: It got a lot of media attention.

MA: Yes, of course. But, seriously, the different diagnostic systems in psychiatry are poor.

AT: So, they don't capture the different firewalls between disorders? They don't capture the complexity of the psychiatric illness.

MA: And if you are looking at families loaded with psychiatric disorders you can see very often that different members of the family have a different diagnosis. If you would have a genetic cause, one gene couldn't be responsible for different diagnoses.

AT: And, also, the name of one or another diagnosis changes dramatically from one DSM to the next. Before 1980 there was no panic disorder. How could you chart the history of panic disorder if in a medical chart, there is no record of that? It's complicated.

MA: Yes.

AT: So, my final question is: do you have any regrets about your career in research you've pursued?

MA: I say, sometimes that I would not do it again, but not because I regret it. The problem is that there are so many regulations now that it is no fun to do research any longer. We had a lot of fun in doing research before. Nowadays you have to submit your proposal for a new research program to a committee that meets every six months ones and in addition one has to comply with all the different regulations. Administrative matters can be very frustrating. Of course there is need for some controls, but sometimes these controls make things difficult.

AT: Is there anything you would like to add?

MA: What else would you be interested in?

AT: Just to know more about your work and you. You've done a great job. Thank you very much

MA: Thank you.

CHARLES M. BEASLEY, Jr.

Interviewed by William Z. Potter
Scottsdale, Arizona, December 8, 2008

BP: I'm Bill Potter, and today I'm interviewing Dr. Charles Beasley* for the ACNP history series. We are in Scottsdale, Arizona. It is December the 8th, 2008. So, Charles, I think we would like to start; if you could just give us a little personal background like where you were born and how you got to the point of entering your psychiatric training.

CB: Yes, I was, perhaps interesting enough, born in Tokyo, Japan. The reason for that was that my father was career military and he actually met my mother who was a civilian employee of the department of the Army in Japan. So, therefore, I was conceived and born in Japan. But, I was only there for six months.

BP: What year was that?

CB: The year was 1950.

BP: Okay.

CB: Being, as we are sometimes referred to, "army brats" or "military brats", I moved around quite a bit into my early adolescence, mainly military towns such as Atlanta, San Antonio, in the United States, and spent a three year block in Germany. I went to high school in Lexington, Kentucky, and I started Yale as an undergraduate in 1968. My first interest in psychiatry, actually, had its origin with the reading of Freud's *General Introduction to Psychoanalysis* over Christmas break of my freshman year, and, I decided that I wanted to be a psychiatrist with a very, very definite psychoanalytic focus.

BP: So, it was already in your mind, to go into pre-med at that time?

CB: Yes, it was.

BP: Okay.

CB: I had actually a very protracted undergraduate career with work in both psychology and extensive work in computer science evolving into work at a quasi-graduate level in artificial intelligence (AI) at Yale.

BP: When was it that the Yale people were involved in artificial intelligence?

CB: It was one of the hot beds of AI research in the middle '70's. Actually, it is a very interesting story. There was still a lot of defense money around at the time; the notion being the desire to develop intelligent weapon systems. Tanks, smart bombs, could essentially be directed by voice command. Stanford was working on robotics; Carnegie Mellon was working on voice recognition; Massachusetts Institute of Technology (MIT) was

* Charles M. Beasley, Jr. was born in Tokyo, Japan in 1950.

working on visual recognition systems and Yale was working on learning and natural language processing. So lots and lots of money, was going into AI research. I view this as the second wave of the glory days of AI. The first wave had been immediately post-Sputnik with an interest in machine translation. Turns out translation from Russian to English is a lot more complicated than word-for-word substitution and following some simplistic grammatical rules. Initial failures in these efforts lead to a greater insight into the extent of complexity of information processing in human.

BP: Okay.

CB: So, this was the second big wave with lots of Cold War defense money.

BP: Was there some sort of subliminal influence from having been in a military family going around? Or, was this just something you got interested in as a student?

CB: It was just an intellectual interest. I had done a bit of computer science work in high school and this was something that was extremely fascinating to me. There was actually some bio-medical AI work going on in the mid- to late-1970s and when I was back at Yale I was involved in this work. Most of the bio-medical work was going on at Stanford. The hardware, on which I was programming as a research assistant, while at Yale, was located at Stanford. There was actually a psychiatric AI researcher who developed an AI model of delusional disorder on the Stanford system, which was sort of fascinating. This AI work was one major side-track of mine that paralleled my interest in psychiatry but still with a very, very analytic bent.

BP: So, what I'm hearing, your interest was in two very different directions. I can see your professors at Yale wondering why you would like to go into medicine when you could do real science. Was any of that at play?

CB: Well, I think that was a question that some had but this was my mix of interests. I always viewed the computer science work as an interesting potential mechanism for validating hypothesis. That was certainly the way people who were doing this work viewed it within early "cognitive science". Nobody was really tremendously interested in developing weapon systems but people were very much interested in hypothesizing mechanism for learning and hypothesizing mechanisms for natural language processing and being able to validate or refute those hypotheses through developing computer systems. The AI modeled those hypotheses and could either validate them as possibly relevant to human information processing or invalidate them. These were the early days of the evolving entity of cognitive science, a field spanning between cognitive psychology and the computer science domain. With the cognitive science AI

paradigm, a program that could perform clever work was not a particularly good program; a good program had to perform the clever work as would the human mind. Brute force searches with perfect memory of all potential moves and counter moves down 36 future move and counter-move alternatives, as a way of designing a chess program, would not be viewed as good cognitive science in AI. That's not how the human brain plays the game.

BP: So, clearly, part of you was thinking of something in research related to the brain, part of you from the very beginning, it sounds like. But, you said also that one point in your life, you were thinking of pursuing a clinical path, including analysis. So, what happened? How many years it took before you decided that you would go more in the research direction instead of becoming a practicing analyst?

CB: Actually, some of my fantasies at that time revolved around potentially modeling psychoanalytic and psychodynamic concepts within AI. Within AI, such modeling could serve to investigate and potentially validate the viability of analytic hypotheses.

BP: So, you were going to pull it all together?

CB: Well, it was narcissistic thinking.

BP: Well, let's see when did you get to the point to begin to have the opportunity to do something beyond thinking about these problems.

CB: I ultimately, received an under-graduate degree in 1977. I did one year of research as a research programmer with my senior advisor, who was a cognitive psychologist AI researcher at Yale, and during that year I was applying to medical schools. This was initially complicated by the fact that I was engaged to a woman at the time. She still had a couple of years to finish her undergraduate degree. Therefore I had a strong interest in remaining in New Haven at the time. My professor was relocated to Carnegie-Mellon at the end of my first year of work with him, and I did another year of work in New Haven in the Department of Neurology, developing a database management system for evoked potential data. So, this work was getting a little bit more bio-medical. I started medical school in 1979 at the University of Kentucky. It had been years since I had done any biological science work, whatsoever, or had to do any work that required lots of memorization. It was an interesting transitional experience for me. And, I thought that I would really hate this medical stuff; that it was just something to get past in order to get to be a psychoanalyst. However, in my second year I really got incredibly fascinated by my Pharmacology course.

BP: Okay.

CB: In the second year of med school...

BP: So, this would have been around 1980.

CB: Yes, this would have been around 1980.

BP: This would have been very early for molecular pharmacology.

CB: The interesting thing about the UK pharmacology department was that we had all of those people, such as Professor Martin, who had actually been doing some of the early psychopharmacology research in the area of opioids at the narcotic hospital and research center in Lexington. There was a collection of great early talents in psychopharmacology. Abraham Wikler had been there but our paths did not directly cross. Professor Martin was Chairman of the Department. Second year pharmacology provided the beginnings of my real turn on to biology and biological mechanisms.

BP: It was early in studying compounds that hit the brain, it sounds like...

CB: And, when the narcotics treatment and research facility closed, a lot of the individuals who were there that were prominent simply moved over to the University.

BP: So, that was a natural move.

CB: And, there began for me this transition of about seven or eight years to a confirmed biological, pharmacological set of primary interest. It evolved through medical school, it evolved through my residency.

BP: I noticed that you started your residency at Yale, but then if I understand you right, your wife got a position back up in Cincinnati.

CB: She got a position in Cincinnati. I moved with her to Cincinnati, which was fine with me, from the perspective that they had a very strong psychoanalytic program.

BP: Do you remember who the chair was at that time in Cincinnati?

CB: Roy Whitman.

BP: Whitman, okay.

CB: It was the last of the very, very dominant analytical chairs. There was a close connection with the Chicago Psychoanalytic Institute, although there was a Psychoanalytic Institute in Cincinnati.

BP: I didn't know that.

CB: My first residency assignment was to the research unit that David Garver ran with his interest in trying to tease apart and sub-type psychosis based on pharmacological response to lithium. He was interested in the concept of lithium responsive psychoses.

BP: And, an analytic department tolerated him there?

CB: Yes, he had a very nice unit going there. The clinical head of the unit was a fellow by the name of Jack Hirschowitz who wound up leaving in my fourth year going to SUNY, Stony Brook.

BP: Were you, yourself, in analysis at the time?

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- CB: I had been during my undergraduate days at Yale.
- BP: Oh, as an undergraduate.
- CB: Almost four years.
- BP: Okay.
- CB: It was a terminated and not a completed analysis.
- BP: Okay.
- CB: Dave Garver's research unit also accepted non-research patients when beds were open with a strong preference for patients with psychosis or non-psychotic bipolar disorder. It was one of the units to which residents were assigned for their inpatient experience. I was simply assigned there at the beginning of my second year.
- BP: Okay, so it was by chance, really.
- CB: Just chance.
- BP: Okay.
- CB: As many things are in life I guess. It was quite interesting, I enjoyed it. I enjoyed the staff. It was a very positive experience for me. Again, I was evolving my interests. We did a lot of long-term psychotherapy as part of the residency. I actually found that it just wasn't for me. I found that I had more of the surgeon's mentality and drive than I did the disposition of a psychotherapist.
- BP: But, if I recall correctly you were a good student. Didn't you win an award along the way for...
- CB: It was one of those residency fellowships of which there are multitudes. The one I was awarded was the Laughlin Fellowship of the American College of Psychiatrists. It was a free trip to Hawaii in 1987 and an opportunity to meet many great individuals.
- BP: So, was it more for academic performance or for research?
- CB: I think it was for cumulative activities.
- BP: Okay, I was just curious.
- CB: I don't think I ever saw the letter of recommendation from the faculty.
- BP: But, at this point in time you weren't actually doing your own research.
- CB: During the fourth year of residency, I did a number of things. I had some interest in neuroendocrinology and built a small study onto David Garver's work studying lithium responsive versus lithium non-responsive mood-incongruent psychosis. I studied the extent to which a blunted TSH response in the TRH stimulation test predicted lithium responsiveness.
- BP: I remember that.
- CB: This work resulted in my first psychiatric publication that came out in *Biological Psychiatry* immediately after completion of my residency. I had some prior publications in the AI literature.
- BP: So, that must have been late 1980s?

CB: That was in 1987 or '88.

BP: Okay.

CB: I arranged a dual chief residency in my fourth year. Part of the time I spent on the research unit, and the rest of the time I served as the director of the residents' clinic for treatment of the chronically severely mentally ill.

BP: Did you get to present the work you did on TSH?

CB: In poster format at several meetings and as several oral presentations.

BP: So, how did you get involved with the ACNP? Were you involved at that time?

CB: That's an interesting story. I was actually at the 25th anniversary meeting in Washington, D.C. As you recall, this was a huge meeting. The residency training programs had been encouraged to have at least one resident attend. Dave Garver was the biological psychiatrist at Cincinnati and the only ACNP member from Cincinnati. I was invited by him to attend.

BP: Okay.

CB: So, that was my first meeting, 22 years ago, and that was a major exciting event for me, with all of the major names and individuals in the field speaking at the meeting; many of the NIMH folks, including you, being very prominent at that time. So, that was a very, very positive experience for me. At that point, I was really looking around at what to do and how to coordinate a dual career family. And, for better or worse, my wife really wanted me to get a real job at that point.

BP: As opposed to a Research Fellowship?

CB: Absolutely.

BP: I wouldn't be surprised if Dr. Garver invited you to take your Research Fellowship.

CB: Dave was actually in the process of leaving Cincinnati at that time and preparing to take a sabbatical.

BP: That's right.

CB: At Cincinnati, I was initially offered a position by the department in which I would be ward chief of Dave's research unit. The unit would have functioned as an acute inpatient unit, continuing its emphasis on treatment of psychosis and mania, and I would have had the opportunity to attempt to obtain research funding.

BP: Okay.

CB: The clinical care versus research focus and prospects for the unit were a bit unclear as neither I nor other department members had appropriate funding at that time. I had been serving as de facto ward chief, with Dave as my supervisor and nominal ward chief, for most of the year since Jack Hirschowitz had left early in that year. But, as late as in March, I didn't have a contract. And, rumor came down that this was not the position I

would get if I stayed in Cincinnati. Rather, the position would be in substance abuse treatment program at the VA. That wasn't too appealing to me. It was sometime in March that I began getting phone calls from an executive recruiter, who I was trying desperately to avoid. My wife and I were tired of trying to find things mutually interesting and we were simply going to take what we had at that time. She had a position in Cincinnati with a multi-specialty group as a dermatologist. But, this recruiter actually tracked me down at home one evening. It was a Friday evening, prior to our having caller ID. I answered the phone and she said, "Do you have any interest in a pharmaceutical research position?" I said, well, perhaps, yes. It was something I had thought about but had no idea how one became involved in pharmaceutical development. She said "well, we have this position in the Mid-West." So, I said, "oh well, it must be for Mead-Johnson." And she said, "no, it's Eli Lilly and Company," and I said, "well what in the world do they do in psychiatry?"

BP: This was in...

CB: This was 1987, March.

BP: Okay.

CB: I said well, let me go explore this. So, I arranged for a first interview with Lilly in less than a week. Following a preliminary interview, Lilly asked me back. I had my second interview that extended over a weekend. About 10 days later I had a contract which I was really happy with. This was about early April.

BP: So, was there somebody that you interviewed with who impressed you at that time? Here was a company you had never interacted with. They called it a research position. Did that sound real?

CB: It did. I became aware that Lilly was in the late stages of developing this molecule called fluoxetine. I was slightly familiar with SSRI's available outside the United States. The position I was potentially being hired into was one for the support of fluoxetine and management of Phase IV research with the molecule. Nobody within Lilly or outside Lilly, really had any notion of what this drug, Prozac (fluoxetine) would do from a social perspective. The reason that I was being hired was that the company believed it needed additional psychiatric coverage for this molecule that was, hopefully, soon to be approved as a medication within the US. Lilly was a company that was very much steeped in antibiotics and endocrine compounds. There had been some psychiatric clinical input into the clinical development of Prozac but it had not been consistent. There had been a lot of strong psychopharmacology input from Dave Wong and Ray Fuller, both ACNP members. Again, I believe the company perceived a need for psychiatrists to assist in further management of the compound

after its US approval. I was hired straight out of residency, along with another individual from Tufts, who had just completed his training. We joined a third psychiatrist at the company who had been hired about six months to a year earlier. This third psychiatrist was actually departing the company, so it was the other psychiatrist and I, straight out of residency, responsible for many aspects of Prozac's support.

BP: So, at this point there was the core, what we call launch package ready, the bare bones of getting the drug into the market.

CB: Not quite. The drug had actually been submitted for approval in 1984. These were in the old days when NDA's progressed very slowly. And, something slowing the review process for Prozac was probably the zimelidone fiasco.

BP: So, maybe you should remind people what that was very quickly.

CB: Well, zimelidone was another SSRI that had become available on the market in Europe prior to Prozac. Many people outside the field mistakenly think that Prozac was the first SSRI. So, there was this European experience with zimelidone. It produced a number of cases of Guillain-Barré Syndrome and was withdrawn from the market. Based on this experience there was incredible concern that this serious side effect was somehow related to serotonin reuptake inhibition. Therefore, within the US, there was a very, very slow review of the NDA for Prozac and progression toward approval between 1984 and 1987. Because of this lengthy course of review, a lot of very interesting additional work with Prozac had been completed prior to its approval that would generally be viewed as Phase-IV research.

BP: That is very interesting.

CB: Some of this work had investigated time to onset of therapeutic activity. Early studies had allowed a dose range of 20 to 80 mg per day. Most patients in these studies wound up on 60 or 80 mg per day. Some very elegant fixed dose studies, investigating the potential minimally effective dose on a population basis were completed in this interim between initial NDA submission and approval. All of this was before my time.

BP: Looking back on this, you were designing studies to learn more about Prozac before it was actually launched if I'm hearing this right.

CB: I came in and began working on the design of studies just prior to the approval of Prozac. There were several small comparative studies that I designed. The largest study that I became involved in was a study intended to demonstrate the long-term effectiveness of the compound.

BP: So, your major input was to the design of that study.

CB: That is correct. There was actually a very nice collaboration with academia. There had been some interest in a very simple study that

would have treated patients for six weeks with the drug and then randomized responders to either continued drug or conversion to placebo. We were able to improve the study considerably with respect to prospectively investigating optimal length of continuation therapy in Major Depression. There was discussion at the time regarding the appropriate length of continuation therapy, as distinct from long-term maintenance therapy. We designed a study to both, to demonstrate long-term efficacy of Prozac and also to prospectively evaluate the optimal length of continuation therapy. The design was fairly complex. Patients were treated for up to 12 weeks and those achieving remission were continued in the blinded portion of the study. During the blinded portion that lasted approximately 50 weeks, subgroups were converted in double-blind fashion, from Prozac to placebo at several time points. One subgroup was converted at 12 weeks and one subgroup remained on drug for the entire 50 weeks. There were two other time points between 12 and 50 weeks when conversions occurred.

BP: So, was this the sequence executed as the maintenance study?

CB: There was one retrospective ad hoc analysis that suggested seven months after remission that was optimal for continuation of the treatment for a given acute episode. That work was the basis for our study design. We wanted to prospectively evaluate the seven month hypothesis. We collaborated with five academic sites in an effort to prospectively evaluate this. It turned out to be a very, very good study. A lot of papers had have been generated out of this study. This study also illustrates an important point when it is suggested that industry withhold data from large clinical trials. The entire data package for that study was actually given to all five academic centers to work with and evaluate. There was prospective agreement, prior to data availability, on a set of six manuscripts with each assigned to a specific investigative site. However, as I said, every site got the complete data set and could work with it, independently or in collaboration with other sites to conduct additional analyses. Published papers from this data set have appeared as recently as last year. Let me see if I can recall the chief investigators: Fred Rheimer, Jerry Rosenbaum, Fred Quitkin, Jay Amsterdam, and John Zajecka with Jan Fawcett.

BP: What would you think: would it be easier or harder to execute such an effort 20 years later?

CB: I'm afraid it would be harder to do. But, this is what I believe to be the model of ideal industry academic collaboration. It was a very positive sort of effort. During this period of time my other activities were involved with the work on what is now atomoxetine. At the time atomoxetine was being developed as an antidepressant. There were a number of studies

in depression with a very high placebo response rate. We actually did some very interesting work in this area that was presented in a workshop at ACNP a number of years ago. Some of this work again involved very positive industry-academia collaboration. Unfortunately, we never followed this work through to publication.

BP: What do you think was the most interesting hypothesis that you were able to test? Was it about the maintenance treatment of fluoxetine, or were there other aspects of the effects of fluoxetine that you had discovered?

CB: Well, there were two things that I guess I was happiest about working on in that period. One was the characterization of Prozac's impact on psychomotor function. There was, I think, a lot of misperception with respect to whether the drug is activating, sedating, based on adverse events as recorded by the investigators during clinical trials. I was interested how these events could be codified using a coding dictionary as required by regulatory agencies and necessary to bring some degree of order and consistency to verbatim descriptions written by many hundreds of investigators. Adverse event coding dictionaries are similar to diagnostic dictionaries such as ICD-9 but contain many more entries. The characterization of Prozac's impact on psychomotor activity, based on the incidences of individual adverse event terms within the dictionary, did not seem to mesh well with what was perceived by the clinical community to be the actual impact of Prozac on psychomotor activity. Dictionaries are a necessary evil within clinical trials, as I said, necessary to bring order to verbatim or free text descriptions of signs and symptoms to allow analysis. All of these dictionaries have their positive sides and their negative sides; sometimes they are overly specific and on the other hand, they are on occasion overly sensitive. Sometimes they lump too many things together and sometimes they spilt things apart that should not be split. So, for example, the dictionary that was being used at the time contained distinct entities of "nervousness" and "anxiety". And, guess what? Getting any degree of agreement from amongst 10 psychiatrists on how you slice and dice these two terms or what the distinctions between these two terms are, or how to assign some free text symptoms to one term and other free text symptoms to the other term, would be, I think, virtually impossible. So, the side effect profile for Prozac, as reflected in the incidences of dictionary terms in the Prozac package insert, did not necessarily line up with the experience of some clinicians. We showed and published appropriately clustered adverse event terms in ways that were truly clinically meaningful. This provided a very clear picture of the drug that really matched well with clinical perception. It showed that the drug was associated with a substantial incidence of relatively mild

forms of activation that was not associated with a large amount, relative to placebo, of severe psychomotor agitation. And, interesting, perhaps paradoxically, it was also associated with sedation, something on the opposite end of the psychomotor continuum from activation. And, there were very clear differences in terms of the dose response relationship for these two phenomena. I was very happy with that work. The other area that, of course, became very, very prominent in 1990 and 1991 was the whole issue of suicide and its possible relationship with SSRI therapy. This topic was clearly initiated by the publication of Marty Teicher that actually described a very specific and unique phenomenon. Marty described a phenomenon with some very, very specific characteristics. There was a quantum increase in severity of suicidal ideation; the method of suicide contemplated within the ideation was quite violent; the ideation was ego dystonic and precipitated dysphoria in the patient; and the patient had no intention to act on the ideation. We developed the notion of using large clinical trial databases, based on post-marketing event data, to evaluate this safety topic by comparing it with Marty's reported clinical experience. This controversial topic and my involvement in it have gone through many waves and cycles since our *British Medical Journal* publication. That paper, or more specifically the position that we have taken has unfortunately often misinterpreted. Simply, what we said in that paper is very clear: the controlled clinical trial data, based on adverse event reports of suicidal acts and scale data capturing marked increases in suicidal ideation, failed to support the hypothesis that grew out of Marty's reported observations. We said nothing less, nothing more.

BP: And, that paper was from what year?

CB: The work was performed mostly in 1991 and I believe the paper was actually published in 1992.

BP: I wonder if you switch to olanzapine where I know you made enormous contributions in terms of research.

CB: Getting olanzapine efficiently developed for the initial indication of schizophrenia was clearly my most exciting development project. Following the introduction of risperidone, there was a very hugely competitive horse race between an Organon compound, sertindole, quetiapine, ziprasidone, and olanzapine that began to evolve in about 1990-1991. In 1991, we initiated our definitive clinical trials with olanzapine and were last in this developmental horse race coming out of the gate. However, olanzapine wound up, being the next second-generation antipsychotic to the market after the earlier introduction of risperidone. After the initial development of that program, I became less and less involved with the molecule.

BP: So, really, it was the efficiency of the program...

CB: There was efficiency but it was directed not just at demonstration of efficacy but probably more importantly at the characterization of the safety profile of the molecule. As part of the initial development program in psychosis, we conducted what was the largest double-blind, controlled clinical trial ever conducted with a psychopharmacological drug, we had 1996 patients in that one trial. Within that development program, we included 2500 olanzapine treated patients and had treated some patients for as long as four years when we submitted the regulatory application. That was a large registration program.

BP: Yes, it was at the time. I want to come back to your major current focus, but along the way I would be interested in tracking how you interacted with the ACNP over those years and what and how that played into what you were doing. And also, when did you actually become a formal member?

CB: I attended almost every ACNP meeting from that original Washington 25th anniversary meeting through the current meeting. I always viewed myself, having been in the industry, as really not a major player. And, I did not apply for membership in the ACNP until 2005 and was elected in 2006.

BP: So, just for the sake of history, was there any work you have been doing that you felt would be of merit for becoming a member of ACNP?

CB: The initial development of olanzapine and my involvement with the topic of the relationship between pharmacotherapy and suicidality have been very important matters. Also, my effort to try to very accurately characterize, in a clinical framework, the safety profiles of molecules has been important, certainly to me. I thought, perhaps, the College might consider these things appropriate basis for membership consideration.

BP: Of course, they were. Clearly you were attending the annual meetings even though you were not a member for many, many years. Was there any special ACNP event that comes to mind in the respect of our history?

CB: You know, I was just thinking about that. One of the most memorable moments was the first debate on the matter of antidepressants, specifically SSRI's, and suicide. It was an evening study group and John Mann was chairing the meeting.

BP: What year was that?

CB: This would have been the 1991 meeting I believe.

BP: Okay.

CB: Marty Teicher spoke and I presented the Lilly data. Most of the audience was rather negative towards Marty's position. This meeting was held just before the major reception, out at the fort behind the Caribe.

BP: Back at the days when ...

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- CB: I spent most of the evening at the reception chatting with Marty although I firmly disagreed with some of his positions. I have no idea what I did to find myself in that engagement. I would not describe that as a comfortable evening.
- BP: But, it was very interesting.
- CB: Extremely interesting. So, yes, that was probably my most memorable ACNP experience but not my best memory. This has been a great place to come to share ideas.
- BP: So, what do you see to come in the next five to ten years in psychopharmacology and the areas you have been most interested in?
- CB: I'm concerned that we are going to see a slowing down of drugs coming into late stage development. I also think that we are going to continue to see more and more novel mechanisms being investigated, and preclinical early Phase I work. But, there is clearly an increasing conservatism on the part of regulatory agencies that I believe is going to impact corporate interest in making major investments in late stage major development programs. I'll give you a very concrete example of this matter not directly related to neuropsychopharmacology, a matter relating to a safety interest with all potential drugs. One of the major areas of safety focus on the part of regulators is cardiac electrophysiological safety, specifically avoidance of approval of any drug that might induce sudden cardiac death through a malignant ventricular tachydysrhythmia, secondary to causing a delay in ventricular repolarization. This position is, of course, quite appropriate. Industry is shying away from compounds that have any hint of the specific cardiac ion channel blockade that is the most common mechanism resulting in delay in depolarization. It is also shying away from molecules that show the possibility of some repolarization delay in early phase development even if the reality or clinical significance of the observation is uncertain. This may or may not be to the detriment or the betterment of public health, but I think we are going to see fewer molecules.
- BP: And, if I understand it correctly, you are on one of these boards that play a very active role in trying to figure this out. I mean you are actively involved in this, right?
- CB: This problem of determining if drugs do or do not delay ventricular repolarization in humans to a relevant extent is one of my areas of activity. I work on attempts to improve the design and methods of the study required to be conducted in human that attempts to address this matter. The study is required to determine if a drug prolongs the QTc interval of the surface ECG. It turns out that this is a whole lot more complicated than most physicians would think because there is interest in very small

magnitudes of change. There is a lot more inherent variability and measurement variability in the human QT interval as recorded by a surface ECG, than we can record in humans. The within subject individual variability, observed in conventional clinical ECG recordings, can be larger than the magnitude of change that if real might represent some degree of safety risk. So, with that variability you get very complex issues with respect to safety, statistics and non-statistical design features.

BP: So, what it sounds like basically, you are sitting in the middle of this big emerging developing risk benefit debate in our society. .

CB: This study and what it evaluates is only one small aspect of cardiac safety. There are many, many other areas of safety that need to be addressed but addressed in an efficient manner in order to continue to bring new medications to patients.

BP: So, this is an ongoing and clearly a very hot area. Can you think of anything else you would like to say to the field?

CB: I am just honored that I've been interviewed.

BP: And, we are very happy to have had you do it and want to thank you very much for taking part in the project. Thank you again.

CB: Thank you.

EVA CESKOVA

**Interviewed by Andrea Tone
Paris, France, June 21, 2004**

- AT: My name is Dr. Andrea Tone and I am participating in the ACNP oral history project. This morning, we are interviewing Eva Ceskova.* It is the 21st of June, 2004. We are at the 24th CINP Congress, in Paris, France. Thank you so much for agreeing to be interviewed. I'd just like to start by asking you how you got interested in psychiatry.
- EC: Psychiatry was, for me, always a challenge, because there are many unknown things about the brain. It was an unknown territory, I would say, it was a challenge for me. It was an adventure.
- AT: Can you tell us a little bit about your background? You grew up in Czechoslovakia?
- EC: Yes, I grew up in Moravia. It's part of the Czech Republic in the south, close to Vienna. My father was a general practitioner (GP) and my mother was a nurse, so, I was educated in a doctor's family.
- AT: So, at what point did you know that you wanted to go to medical school?
- EC: You see, I decided to go to medical school quite early. At first, I didn't know what to do, because I was afraid of not being able to be like my father. He was a fantastic doctor and I wanted to be also very good at something. But finally I decided to study medicine at Masaryk University of Brno. During my studies I was thinking about specialization. Because I don't have the necessary skills I couldn't do for example surgery. It's a very hard job. So, I was looking for something challenging, and it was psychiatry. And, also, my best friend went through a psychotic episode. It was, for me, a big experience, and, so, I decided to go into psychiatry. In fact, I started to go to the Department of Psychiatry at the University of Brno in 1967 while I was still a medical student. I continued in the Department as an assistant physician and rose on the academic ladder to become associate professor, professor and head of the department. Looking back at those years, the best position for me was the position of associate professor because I had a lot of time to do work that I felt was useful. It was wonderful. Now, I have many administrative responsibilities and it's not easy for a woman to be in such leading position in the Czech Republic.
- AT: We were talking about that the other night. Take me back to when you first started going to medical school. Did a lot of women go to medical school at that time? Did a lot of women choose psychiatry?

* Eva Ceskova was born in Znojmo, Czechoslovakia (Czech Republic) in 1946.

- EC: Not a lot of women. Women choose usually less large specialties, and in general usually don't choose science. There might be historical reasons for that in my country; men want to have women home with the children. It's changing. The younger generation has started to change this tradition. But, it's quite difficult to change the tradition because it's pretty hard to find any help for housekeeping.
- AT: Were you regarded as kind of a revolutionary in the 1950s? What was the attitude toward you when you started out as a female psychiatrist?
- EC: I was very happy with my colleagues in those days. My mother was looking after my children. So, it was easy for me. And my father supported me, economically.
- AT: Why did you choose the particular area of research you pursued within psychiatry?
- EC: I loved chemistry, biology and I succeeded to get a WHO scholarship in the USA in 1980. It was a scholarship in psychopharmacology at the Tennessee Neuropsychiatric Institute of Vanderbilt University under Thomas Ban. And I found psychopharmacology challenging and interesting. I was delighted to follow the progress in the field. We now start to know the brain, what the brain does, and this is very exciting.
- AT: The clinical trials you were engaged in, were they in schizophrenia?
- EC: They were investigations in psychosis, schizophrenia, and affective disorders primarily. .
- AT: Can you tell us about your Nashville experience?
- EC: My first impression about the United States was that it's a big place with many, many cars. People were smiling most of the time, and most people were hospitable. They took care of me, probably because it was rather unusual to see a lady from Czechoslovakia who decided to come to Vanderbilt. I was thirty-two at the time, married with one child. So, it was fun.
- AT: Did your child come with you to the United States?
- EC: No..
- AT: Did you like Vanderbilt?
- EC: Yes, and I was working hard. But I had also an opportunity to travel around the United States. My favorite city was San Francisco. I loved it more than New York. San Francisco was for me something very special.
- AT: So, what would you say you benefited most from your stay in the United States?
- EC: The access to information. I could get whatever scientific journal I wanted. It was fantastic. I made so many copies of papers that I sent two big boxes home. In the Czech Republic I couldn't get information, scientific information. So, I was so happy about that. It helped me to write

my thesis about the treatment of manic states. So, it was wonderful. I spent all the weekends in the library.

AT: When you were in the United States, what would you say the chief differences were in the treatment of psychosis? Is there such a thing as a Czech tradition in psychiatry that's different from, say, the American tradition or the UK tradition or the German tradition?

EC: I don't think so. You see, in the United States, forty years ago, there was a strong psychodynamic movement which possibly led to a different approach in the treatment of psychosis, but, basically, now, the treatment of psychosis is the same here and in the Czech Republic. We have the same drugs in Europe, especially in the Czech Republic that you have in the United States. Since the FDA rules are stricter than the rules of our drug regulatory agency, we have some drugs earlier than you do. But, the treatment approach is the same. In the United States you have some institutions at the top which are able to generate the necessary money to get good people and to create for them a terrific condition for scientific work. In my country this is not the case. As Head of the Department I have to do everything myself. Since my secretary does not speak English, I have to write most of my letters myself.

AT: Could you tell us something about your Department?

EC: In the Czech Republic there are only six university departments of psychiatry. My department has one hundred-twenty beds. Our department of psychiatry is quite new. It is in a very nice thirty-five years old building that was designed for a psychiatry department. We have the neurotic patients on the top floor. The second floor is for psychotic disorders and so on. It is a wonderful building with teaching facilities, labs, and everything. We have a division for psychotics, a division for children, a day clinic, a division for neurotic disorders, and a crisis intervention center. It is quite difficult to manage it.

AT: Administratively?

EC: We have to do many things that are waste of time and take us away from patient care. I would like to spend more time with patients. I love my patients but I have only one-day for outpatients, for my faithful patients. I would like to teach more. I love to teach. It's my hobby I would like to continue teaching as long as possible. .

AT: Are you in contact with the other department heads? .

EC: Thirty-seven years ago, when I started, there were not so many psychiatrists in the Czech Republic and we all knew each other. Fortunately, all the heads of the departments are my good friends. It has some advantages and some disadvantages. The Czech Republic is a small country.

- AT: What would you say the chief change has been to the practice of psychiatry with the unraveling of Communism? Did that have any impact on treatment or psychiatry as a profession?
- EC: In my opinion, no. But a great advance is that the young psychiatrists can travel, can go abroad and can get much more information. So the possibilities that are changed; they are much better for young doctors now. But, basically, we are treating patients in the same way.
- AT: Is it harder for patients to get treatment for economic reasons?
- EC: Treatments, hospitalization, drugs are still free of charge but this is changing. There are discussions in the Czech parliament that the patient should contribute or to pay something for their hospitalization..
- AT: Now, I read, it's possibly wrong, so correct me if I'm mistaken, that in Communist countries psychiatry was politicized and it was questioned why people should have psychosis, depression, or anxiety when Communism is sort of taking care of everything. Were these disorders concealed for political reasons, or, were people if they suffered from these disorders treated as compassionately as they were in other countries?
- EC: It is exaggerated that psychiatric diseases were concealed for political reasons. . But, it's true that now, people are more informed about psychiatry, generally. The Czech Republic is more of Central than Eastern Europe and has a long tradition of excellent education, including medical schools. Communism was not able to spoil that. There are always some people who are suffering from personality disorders, who are very difficult to treat under whatever regime.
- AT: You don't think there was a problem ever with under treatment or failure to treat people, in general, because psychiatry was seen as at odds with Communism?
- EC: I don't think so. It is related more to the attitude towards psychiatry in general, but this is changing. For example, many depressions are now treated by GPs, and GPs have access to some psychotropic drugs. They can prescribe antidepressants. So, the situation is changing and psychiatry is integrating with general medicine. We need collaboration also with other specialists. An obvious case for this is depression. We know that many somatic illnesses are connected with depression and vice versa. So, there are many common factors.
- AT: A lot of research in psychiatry in Western Europe and the United States was industry driven. How does that work in the Republic of Czechoslovakia?
- EC: It is the same.
- AT: How did you become Chair of your Department? How long have you been Chair?

- EC: I was appointed Chair in 1992, ten years after the velvet revolution. At that time I was forty-eight years old and very naive. I had two priorities: my family and psychiatry. I was associate professor of psychiatry, and I have never been a member of any party. So, I was the only one who fulfilled the criteria for the position. It was funny. I was afraid of it, really, I was.
- AT: How come? Why were you afraid of it?
- EC: Because it was a great responsibility. My predecessor was my teacher, an excellent psychiatrist. Our department was one of the best in the country. But, I'm quite happy now, because I think I've educated several young psychiatrists, who will be able to continue my work. I can retire and I'm sure they will be successful. I was the only woman in the Czech Republic who became Chief of a psychiatry department.
- AT: You were the first. Did you feel that added a certain burden, that you were a role model? That you had to be a pioneer for all the women?
- EC: You see, I had no idea what it was about. I was associate professor, so I had to be appointed professor first to be accepted as head of a department by the other department heads. And it was a very hard job to become accepted by them.
- AT: Can you tell us more about that, how it's been to be the first woman doing this?
- EC: Being a woman has also advantages. For example: I could say what I wanted, because men, in our culture don't take woman talk seriously. I'm fifty-eight years old now; I'm old enough to say what is on my mind. And as I told you, the chiefs of all six departments in the Czech Republic are now my friends. We know each other very well. So, they accepted me. It is funny that my husband has never accepted that I have the position of professor of psychiatry.
- AT: What do you mean by that?
- EC: He doesn't accept that women could be good in such a position. My husband thinks that women doctors are not good and women psychiatrists are the worst.
- AT: How come? Why are women psychiatrists the worst?
- EC: In the Czech Republic, as everywhere else, women had to fight for their rights. And we were successful. But thinking is changing only slowly. In the United States women are much more emancipated, although the emancipation of women seems to me is exaggerated and commercialized.
- AT: That's great. Do you think that there are a lot of men who like your husband still wrestle with the role of women?
- EC: Yes, especially in the older generation. At home I have to do everything. I look after two children; I have no time for TV, books, but it was my choice.

Now my son is 21 and my daughter is married. I am a grandmother so I feel more comfortable.

AT: Maybe it's harder for women because they have more responsibilities to juggle. It's interesting because the perception in the west is that, especially, during Communism, women and men were educated equally. They were encouraged equally.

EC: Oh, it's true that they were educated equally.

AT: Looking back at your career, which still seems like it's got a ways to go, if you're only fifty-eight, what are the contributions that you've made that you're proudest of?

EC: I think I'm proud of that I succeeded to educate and train many psychiatrists. Unfortunately many psychiatrists of the young generation are interested only in making more money. Many of us from my generation feel that only a few are ready to make any sacrifice.

AT: But, for you, there's something about a passion or calling. Do you think you've been able to inculcate that sensibility in the younger generation, or at least instill in them?

EC: Oh, yes. I think to be a doctor one needs to be of a certain type of personality. The same applies for teaching. You can't teach if you don't like to communicate.

AT: Any regrets, looking back? Are there thing you wish you'd been able to do that you haven't been able to do?

EC: I don't think so.

AT: Looking at your career, do you have any other things you wish you had been able to do but weren't able to do? Regrets?

EC: I don't think so. In the Czech Republic we have more connections with Germany, Austria, France, also, historically, and in terms of the quality of education, than with Eastern Europe. .And, so, I feel being more West than East. Yet, I had also opportunity to participate in an international clinical trial with clozapine organized by Russian psychiatrists.

AT: So, you have opportunity to collaborate in studies organized in the West and in the East.

EC: I had seen the US and Russia, two very big countries, separated by the Iron Curtain. In the United States, I bought a newspaper and I have read the stupidity about Russia and in Russia, it was the same vice versa. Now, it's great that we have communication with both. It's really a big advantage.

AT: The opening up of the knowledge.

EC: Yes.

AT: Is there anything else you'd like to add before I stop this tape?

EC: No, no, no, thank you very much. I have not so many opportunities to practice my English. I can read very well, but to speak, it's complicated for me. That is all I have; nothing is left.

AT: Thank you so much. I think, in some ways, Americans are embarrassingly behind in that we do not have the same language skills that people in other countries have. We just assume that English will take us everywhere. It's very arrogant.

EC: No, I don't see it like that.

DENNIS S. CHARNEY

**Interviewed by Andrea Tone
San Juan, Puerto Rico, December 7, 2003**

AT: My name is Dr. Andrea Tone. We're at the 2003 ACNP Annual Meeting and it is my pleasure to be able to interview Dr. Dennis Charney* for the ACNP Archives. Thank you so much for joining us. Let's start with some basic background about you. Tell us about your upbringing.

DC: I was born in New York City. I lived in New York five years or so, then moved out to Long Island, where we lived in Merrick, Long Island, and then North Bellmore where I went to high school. My father was an engineer; he is now retired. My mother was a guidance counselor secretary, so they generally both worked full time when we were growing up. I have a sister who is three years younger than me who is a nurse and lives in Boston. I have a brother who is five years younger, who is a dentist and lives outside of New Haven, CT. It was a very positive family environment. I remember when I was interviewing for psychiatric residencies which, back then tended to be almost like a psychiatric interview per se, the interviewer kept asking me, "Well, what about your family?" And I kept saying, "It really was a good family". We had a good time growing up. We were very lucky in that there were no major traumas. There was just a very positive family environment. I was very much focused on athletics, so sports were very important for me. I was a basketball player. I was a star basketball player; I was ranked among the best in the United States, you know the various ratings that they would do. So that was a very important part of my life. This was in high school. So, that defined me quite a bit in high school. School, course work was really not a priority. I did okay, but I didn't do great. I was kind of an average student in the advanced classes. They give you a test in the 7th grade to determine your aptitude. And my aptitude was good, and so I got in the highest-level classes. But I wasn't a really hard worker. I was really working at basketball in those days. I still play quite a bit. And another element growing up was that I met my wife when she was 14 and I was 16, so we were high school sweethearts, and that was it. You know, believe it or not, we didn't date anybody after that, since she was 14 and I was 16, and that's been a great relationship. We have been married now almost 32 years. We have five kids.

AT: How did you get interested in medicine?

* Dennis S. Charney was born in New York City, New York in 1951.

DC: I didn't have a love for science growing up. Like I was saying, I really wasn't focused that much on school work. But when I got to college - I went to Rutgers, in New Brunswick, New Jersey - early on it became apparent to me that I was not going to be able to be a pro basketball player. I realized that there were people that were another order of magnitude better than me. I should have known that even in high school, because you would go to basketball camps where they would bring in people from all around the country, and I would do well there, but there were just some guys that were amazing. But you don't realize that until you play against them. When I realized that I couldn't be a pro, I had better think about something else. I tend to be a person that focuses and works extremely hard at what I decide I want to do, and so I decided to enter pre-med. Now why I did that? I'm a little embarrassed to say, but it was more that my family said being a doctor was the right thing. I did not, in the beginning, have a burning desire one way or the other. It wasn't like a strong pressure. It was like, gee, my grandparents were born in another country. They were born in, depending on the side of the family, either Russia or Austria. And then my parents also were the first generation into the US; my father went to City College in New York because he was poor and that was free. And my mother's side of the family was not wealthy either. My grandfather, when he came over was uneducated, and he became a butcher. He was a butcher in the Bronx. And my other grandfather owned a grocery store. So, their offspring, my father, became an engineer. And so, to their view, becoming a doctor, well, it's an amazing thing when you look back on their parents. And so I bought into that belief that maybe it would be a really good thing. So I entered pre-med. And then I started to enjoy it. I liked the sciences. I did very well in college. I still played sports, but I didn't play basketball. I rowed crew, because I always needed to do something athletic. And I still do. Competition is very important to me. But I wasn't as focused on as I was thinking about it all the time, which I did with basketball. So, when I rowed crew, I went to practice, had a great time, but then when it was over, I was studying. That's pretty much what I did. I put all my energies into those two activities. Then in 1973 I went to med school at Pennsylvania State University. I chose the Penn State Med School because it was known as a med school that emphasized the humanities. It had, I believe, the first humanities department in a medical school, which was unique. And they were dealing with ethical issues early on. They were also known for training physicians who were very much in tune with the patient. Primary care was a focus of the med school. I could have gone to many different med schools. I saw myself becoming a physician, perhaps like in internal medicine, a family doctor,

and then going to the Peace Corps. But it didn't turn out that way. I developed a relationship with the Chairman of Psychiatry, which is fairly unusual as a medical student. It started from when I was a first-year medical student. He was a researcher, so I got involved in his research.

AT: How did it happen?

DC: I don't remember actually how that literally happened. Basketball did turn out to be a connection there, though, he loved sports. He loved basketball. He wasn't an athlete himself. So, I ended up coaching his kids in the local basketball league. In part, that was how we developed the personal relationship. I don't actually remember how, but literally, in the first year, I connected with him. What was the sequence of that, I don't remember that. But, it was quick. And so I got involved in his research team. I became a research assistant part time and found that I liked research. His area of research wasn't the area that I eventually focused on. He did sleep research. But it turned out that I really liked research. It had elements to it that related to what I found enjoyable in athletics; it involved working with a team. I liked that a lot. And I also liked the idea of trying to discover something. And even the element of competition in trying to discover something. By the end of the first year, the Peace Corps was out and science was in. I felt pretty sure at that point that I wanted to become a scientist, a researcher. By the end of the second year, I was committed to psychiatry.

AT: Can you tell us something about your teachers in psychiatry?

DC: The group was pretty eclectic, meaning that they tried to teach you psychoanalytic principles and they tried to teach you about the brain but that was not nearly where we are today. They tried to teach you how diagnosis was being made, and this was at the time when standardized diagnosis was first being developed, like the DSM-III. So, it was eclectic. I was fascinated by the idea of a biological basis of psychiatry. But at that point in time there was hardly any research in that area. So, it seemed like a really exciting new area that you could make an impact very quickly. On the other hand, I was still fascinated by Freud, and I still am. I think Freud made fundamental discoveries regarding the development of emotion, the different components of emotion, and that he was right on a lot of counts. I don't think his therapy turned out to work really well, but his concepts about the mind were tremendous. So, I was interested in Freud, and for awhile I was interested in how to take some of Freud's concepts and understand them from a biological point of view. Freud, himself, was very interested in biology. But the tools, back then, at the turn of the century, were minimal. So I did go at the end of the second year to the Menninger Clinic, Topeka, Kansas, which is known as a bastion of

psychoanalytic thinking. Karl Menninger was a very famous psychiatrist in the 1940s and the '50s. So I thought that I would learn one way or the other whether I really believed that psychoanalytic practice had validity. So I went there for six weeks. My wife and I went out there, to the middle of the country, over the summer. They had a special six-week clerkship for medical students after their second year. And it was that experience that convinced me that I did not want to focus on psychoanalysis. They would teach things in a way that they were very sure that they were right. And I would be asking, "Well, how are you so sure? I mean, what is the evidence"? And there was no evidence. I was asking the best people in the country, and I didn't feel that there was enough evidence, particularly in relationship to the practice of psychoanalysis, that type of treatment. Observing the treatment and how the treatment was being targeted for certain types of disorders, I just didn't see an evidence base for the field. There were no clinical trials. There was just no evidence. It was a little bit like the emperor had no clothes, and when I left that program - I had a good time, they were nice people - I left convinced that that was it.

AT: What were you looking for?

DC: I was trying to understand on what emotions and feelings and cognition are based on, how the brain works.

AT: Was this a divisive issue?

DC: It was not a divisive issue where I went to med school, because the Chairman, Tony Kales, was a sleep researcher, which is very biologic. He was doing EEG recordings, and he was one of the discoverers of the different stages of sleep, like REM sleep and stage 1 to 4. He was very biologically oriented. So, in terms of my experience in medical school, that was very consistent with the emphasis of the leaders of the psychiatry department. And then I went to Yale. I did my residency at Yale. I thought Yale had some of the best biologically-based researchers. Yale also had a very strong psychoanalytic department. At the time I went to Yale, I think it was felt to be the best place to be trained in psychiatry in the United States, because it had a combination of outstanding basic scientists, clinical researchers, and people who were quite well known in psychoanalysis. There was a healthy debate within the department with very smart people on both sides of the fence. So I did my residency there.. That was a great experience. I had some tremendous mentors; George Heninger, in particular. I became involved in research very early on. In fact, one of the premier researchers in biological psychiatry at that time was named Jim Maas. He was a leader in that he helped define how we would measure the function of the metabolites of monoamines in the brain, like norepinephrine. And he also had some groundbreaking ideas

on how to assess receptors in the brain. Those are protein targets for neurotransmitters. So, for example, adrenaline and norepinephrine interact with the receptor to have its effect. He had some really important ideas there, and so, when I was still in med school, and I knew I was going to Yale, I wrote Maas a several page letter about the idea I had about doing research. At the time I wrote the letter I didn't think it was unusual. I do, in retrospect, feel it was pretty unusual. Pretty bold, having a med student just write this letter out of the blue to this eminent researcher. And he wrote me back a short response in a month or so saying it was an interesting idea, but it would probably cost too much money to do it. But that gives you a little bit of the flavor that I was assertive. At any rate, the Yale residency was a great experience. It turns out that Maas left shortly after I got there, and that turns out to be, in a way, a lucky break for me. I was interested in understanding the biology of depression and anxiety states, and Maas was a leader. So, when he left there was a hole in the department for that area that enabled me to have a leadership position very quickly after his departure.

AT: Were you still a resident?

DC: Yes. Well, you have to be trained to be a clinician, and I enjoyed my training. But I was motivated right from the beginning to do research. You should interview George Heninger and he will tell you. George is one of the best mentors, I think, our field has had. He's not as well known as a scientist in terms of discovery, but he's a tremendous mentor. He was a senior person there at Yale when I had started as a resident. I kept bugging him when I was a first-year resident. See, when you are a first-year resident, you are mainly an intern. You do medicine and surgery and neurology, and you rotate through all the other specialties. In fact, you don't even do psychiatry in the first year. But I kept calling George up and I'd say, "Well, can I attend the seminars? I want to get involved in research." And I'm sure he was thinking, "Who is this guy? Who is this guy who's calling me up"? And he found out eventually. But that was the start of our relationship. So, yes, I did start right away. I wasn't able to do research in my rotating internship year because you're on call every second or third night, and you're not even rotating through psychiatry. But I did start research in my first psychiatry year.

AT: Would you tell us something about the research you were involved with? Was it in affective disorders?

DC: Yes, I've been very consistent in that way. I was always interested in depression, bipolar disorder, and the various anxiety disorders like panic disorder, well, mainly panic disorder actually in the beginning. When I started out in 1978, PTSD, Post Traumatic Stress Disorder, wasn't even

a diagnostic condition according to the diagnostic manuals, per se. So, I didn't get involved in that until a little bit later. But it was the same general focus using whatever tools were available to understand what might be going wrong in people who suffer from those illnesses from a medical point of view. What's the problem in their brain? And how does that interact with their environment? And how does that interact with the genetics? We had good models at that point. I felt at that point, that schizophrenia was a much harder, much more intractable disorder to begin to study from a biologic point of view. We had some pretty good animal models, particularly of anxiety, that gave us clues as to where to look in humans. We had some clues what neurotransmitters, for example, or neuropeptides, might be abnormal in patients based on the laboratory animal research. So there were paradigms that were available. Given the research techniques and the research hypotheses that were available back then, I felt that focusing on those disorders would lead to more rapid progress; understanding the disease, identifying the pathogenesis, the etiology and, ultimately, discovering the treatment. I loved Yale. Still do. It's a great place. I wasn't really looking to leave. As I mentioned before, I had great mentors. I had been mentoring a lot of people who have gone on to do important things in our field. So, I wasn't actively looking to leave. I felt some limitations to become apparent at Yale in terms of some of the techniques that were available. For example, positron emission tomography (PET) imaging program, needed improvement. And if you didn't have a strong imaging program - at that point, in the late 1990s or early 2000s - you were ultimately going to have a problem. So that was one issue that I was concerned about. We were trying to fix it, but I was concerned about it. The magnetic resonance imaging program was also somewhat limited in terms of the number of magnets that we had. So those were some limitations, but I wasn't actively looking at that point for another job. However, NIMH came to me. They had decided that the intramural program needed some new people; needed some more energy. At that point, I was the Chair of the board of scientific counselors for NIMH. That's an outside group that looks at the functioning of the intramural program. So, I was aware that in spite of some excellent, outstanding people there, the program wasn't reaching its maximum potential. The beauty of the intramural program is that you are given money to do your research. You don't have to write grants. So you have much more freedom in terms of what you can do. It doesn't have the same degree of peer review process that you have when you have to apply for grants, like when you are at a place like Yale. So NIMH came to me. Steve Hyman was the director at that point, and said that they would like

you to develop a program of research in mood and anxiety disorders in the intramural program. They basically asked what would you need to do it. And I told them what I needed and I got all of it, so we ended up hiring 15 or 17 new people from around the world to come. We had the best imaging set up in the world. The genetics was outstanding. So, from a professional point of view, it was perfect. And it actually has turned out to be that way. Your limits are your imagination in terms of what you can do. It's not really resource limited. I made decisions kind of quickly and didn't ruminate about them. It just seemed like a really good thing to do for me professionally. I made up my mind quickly there. I wasn't using it as leverage to get things from Yale, because, really, Yale couldn't give me what was being offered by NIMH. The resources weren't there, even if they wanted to purchase new things or so forth, they couldn't buy as many PET cameras as NIMH has. They couldn't find the money to have me hire 15 new scientists who would develop their own research labs, or the space; it just wasn't practical. So I didn't really negotiate with Yale to keep me. They tried to do it, but I just said it's not possible. So, I was gone.

AT: Did you have any misgivings?

DC: No misgivings. Now it wasn't easy on my family. My family was happy in Connecticut. My two youngest kids were in high school. So they had to move in the middle of high school. And my wife is a pre-school teacher. So she had to find another job. So, they came. It didn't cause family discord, but I wasn't super popular for awhile.

AT: Did your wife work at the time?

DC: My wife didn't work full time until our youngest went to kindergarten. The kids are all close together. They're 18 to 25 now; we had five kids in seven-and-a-half years. So, I guess that would mean that since the first one went to kindergarten about five, my wife was a full-time mother for the first 12 years of having kids. And she is totally un-conflicted about that. We would have had more kids, but we basically ran out of time. So that was naturally like hand in glove. I wanted a big family but that would not have been possible. My wife is a born mother, like I said, so it worked out great.

AT: Would you tell us something about your activities and research at NIMH?

DC: Research at NIMH is based on a peer-review process. It's not so tied to the money. When you have a research project you want to do, you write it up in standard format. It gets submitted to an intramural scientific review committee who comments on it. Very rarely will they say you can't do it. It's not like the extramural grant program where you either get the money or you don't. But the NIMH committee will give you feedback. They'll

send it to some outside people. So it does keep you on your toes writing up your projects and knowing that peers are looking at them. But it's not the same pressure as a grant being funded or not. And then it does go to an IRB and an ethics committee. They make sure it's ethical and so forth. The vision that we brought to the NIMH was to create a basic science program and a clinical research program that would simply facilitate the discovery of new treatments, because they are desperately needed in our field. So, that became a major focus, new medication treatments; also to discover the genetic basis of the diseases and relate to the genetics to what is going wrong in the brain. So we were looking at different genes. We then used the techniques of brain imaging to see how your genes affect how your brain handles emotions and so forth. We recruited people who were experts in the basic science areas who could develop new models in the laboratory for these diseases, and identify new molecular targets for drug development. We hired human genetics researchers who would be able to look at all the genes that have been identified with the human genome project. We brought on expert neurimagers. Then, finally, we brought in people who were very interested in doing clinical trials with novel treatments. So it was a broad spectrum approach, but with the ultimate aim of discovering new treatments and cause of disease.

AT: Did you aim for treatments directed to the genetics of the disease?

DC: Well, in the 1970s and '80s, we couldn't identify genes; the techniques were not there. The techniques we had were very slow. What took a year to do two decades ago, now takes two days. There has been an explosion of genetic techniques in the last two decades and also of human genetic laboratories to identify different genes and relate them to diseases. It became apparent to me in the early to mid 1990s that genetics has to be a major focus of research. . We finally had the capacity to do the studies we needed to learn enough about the cause of diseases. We know that in many of our diseases, genes play a role. They are not destiny, but they play a role. The other important initiative was brain imaging. That became available a little bit before the genetic revolution. Compared to when I started in the field - when we didn't have brain imaging and human genetics techniques - and now, two decades later, it was a totally different world. So, it meant you did have to keep learning as a scientist to be able make the right decisions. It was clear to me that we needed to image the brain, and to look at the genes to be able to relate how what we saw to functions. I have never met anybody that says genes don't play any role in psychiatric disease. I think it's a matter of how much of a role they play. Do we know how much of a role they play? We don't, yet. We know that depending on the disease and depending on the gene,

by looking at both, will give you information about the degree of susceptibility. As will other genes give you a certain degree of protection. So there are risk genes, susceptibility genes, and then there are genes that will provide protection, perhaps, against disease in the context of, in our field, stress. In other fields of medicine, there are genes that will relate to protection against certain infections. You know, that's how natural selection takes place. If you have a gene that protects you against an infection that is endemic in where you live, say in Africa where it may be more of a problem, then that gene will be selected for very quickly in terms of the process of evolution. In our field, it's a little bit slower because we don't have genes that have such a clear-cut effect in influencing mortality in a very potent way. They do in smaller ways. It's a little bit harder to identify genes that protect you, but we can now start doing that. There are paradigms now that enable you to look at one's genes and look at the environment in which somebody was raised and lives in, and to see what the interaction between those two are in terms of vulnerability to getting a psychiatric disease.

AT: Would research in genetic environmental interaction also help in removing the stigma of mental illness?

DC: Yes, I think by having information on genetic environmental interactions in the news, mental illness definitely has become less stigmatized. To me the best recent example was an article in *Sports Illustrated* on depression and anxiety in athletes. Some athletes like Terry Bradshaw, who was a Super Bowl winning quarterback for the Pittsburgh Steelers, came out and said, "I've been depressed for decades. Even when I was winning the Super Bowl, I was having problems with depression". Ricky Williams, who was the leading running back in the NFL last year, came out also and said that he had severe problems with social anxiety disorder. There's a great quote in that article in which Ricky Williams says that "If you have a broken bone, they get you the best orthopedic doctor, but if you have a broken soul, they think you are weak". But the fact that there was an article written about it in *Sports Illustrated*, in which they tend not to write articles that emphasize weakness, I think, is an example of where we have gotten by now and where we're going in terms of stigma. It is very helpful that prominent people who are highly respected in our society come out and say, "I've had these problems; I'm not a weak person; it is a disease like any other; you can get better; you should get treatment too". The other reason for less stigmatization is that we are learning more about these diseases. I think that if you look in the history of medicine, that when diseases are not understood, there's more magical thinking about the cause of those diseases. When we did not know that it was

genetic and what is going on in the brain in depression, it was easier to say, you know, you're weak and this is no disease. But now that we have much better understanding of the illness, it's easy to break down barriers of stigma.

AT: What proportion of people in the general population suffers from mental disorders?

DC: If you ask how many people in the United States currently meet a criterion for one of those disorders, it's about 40 million people. And that number obviously goes up when you include illness over a lifetime. At the moment, the current number of people that have mental disorders is around 40 million people.

AT: Where do these numbers come from?

DC: They come from surveys.

AT: What about the effects of treatment?

DC: We do have effective treatments. The serotonin reuptake inhibitors, like Prozac (fluoxetine) and Paxil (paroxetine) and Zoloft (sertraline), there's about five or six of them, are a class of antidepressants and anti-anxiety medications which are very good treatments. They help a lot of people, and they're very safe to give. In general, they're well tolerated. The fact that they are effective and they're well tolerated is the reason why, as a class of medications, they are the second highest in terms of sales. It means doctors are prescribing them for patients second to cholesterol-lowering medications. While there are many reasons why drugs are sold and doctors prescribe them, I think one of them clearly is that they work and they're safe. So that's true for this class of compounds. They help many people. They're what we call broad spectrum. They work on depression. They work on various anxiety disorders as well. But they're not perfect. The majority of patients still have symptoms in spite of taking these drugs. They're not curative for most patients, but they help. They make things more bearable. They improve functioning. So in that sense, we need to do a lot better, discovering better medications, more effective medications, in particular, for depression, bipolar disorder, panic disorder, PTSD, and so forth.

AT: What are your thoughts about advertisements on mental illness?

DC: First I think those ads have been very useful. We were talking before about stigma. That's one way to break down stigma. If there can be advertisements about depression and anxiety on TV, then maybe they're no longer seen as illnesses where you are just a weak person, who should be embarrassed about having the disease. So I think those advertisements have served a tremendously positive function. Not only for patients who can now admit and say I think I have what I saw on TV or what I read on

the internet, but also for the public at large; ads have served a very useful educational function, even though they are funded by the pharmaceutical industry. I disagree with Healy's comment that drugs don't work and that our treatments are no better than in 1900. That's just a false statement. I think he must be saying that to get a rise out of people. They do work. They're not perfect. Placebo-controlled studies do show that they are better than a placebo in a number of ways. The effect is not huge when you do a short-term trial of eight weeks, when you compare the available serotonin reuptake inhibitors versus placebo. But they do pass muster in terms of what is required to demonstrate that a drug does work. To a much larger degree, and a very clinically relevant degree, drugs prevent relapse back into depression in patients who are doing okay. If you compare the ability of an SSRI versus placebo to prevent relapse in somebody who has just recovered from depression, the separation in regards to those two treatments in regard to efficacy is very large. There's really no doubt that they are extremely useful. I'm a clinician, too. So I've seen patients get better, and I would be very unhappy if we didn't have these drugs available to treat patients.

AT: What about non-pharmacological treatments?

DC: You consider them in collaboration with the patient. In general, if somebody has a depression that is mildly impairing, if patient is dysphoric, unhappy, and not getting the usual enjoyment out of life, but is not suicidal, I would discuss with the patient various treatment options. There are, some psychotherapies that work in these cases as for example, cognitive behavioral therapy (CBT), interpersonal therapy. I ask the patient, "Would you like to try that first and see if that is helpful to you, or would you like to try a medication?" I would go through the various medications and their side effect profile. I would work with the patient, by asking the patient, "what would you rather do"? So in the milder form of illness, the patient as a consumer is, I think, a very useful concept. If somebody is more severely depressed, or if they are suicidal, for example, then I will emphasize doing both and would say: "You know that we've got to get you better fast. We don't want you to hurt yourself. You're really suffering. You're not doing well at work. It's impairing your ability to be a parent". In that patient, I would emphasize doing both by saying, "You know psychotherapy can be helpful. The way you think about yourself and your environment and your family is affected by you being depressed. Let's work on that. CBT does that, for example. Interpersonal psychotherapy does that in terms of relationships. But let's also start the medication too, because time is important".

AT: What about ECT?

DC: ECT is an option. It's the most effective single form of treatment for very severe depression. Unless it was a true emergency, it is very rare that you can't provide a person a safe environment while you're waiting for medication to work. But, I generally reserve ECT for people who have clearly not responded to a number of different medication and psychotherapy approaches.

AT: Do patients prefer pharmacological to other treatments?

DC: It hasn't been my experience with the patients that I see. But, then, some patients don't want to take medication. They don't like the idea of it. They do have side effects; about 30 to 40% of the patients who get an SSRI have a reduced sexual performance. There are patients, of course who say just give me the pill, doc, I don't want to talk about anything. But there are other people on the other end of the spectrum who say, you know, I don't want to take medication. I think there are people on both extremes. But the vast majority of people that I see just want to learn what their options are, what the side effects are, how long it will take before it works, and they work with you on making a decision.

AT: Is the situation the same in family practice?

DC: The patients I see are, in general, involved in research. But my impression is that it's terrible for patients with mental illness, because of lack of parity in healthcare coverage, so that it's harder to get treatment. It's harder for them to afford treatment. It should be covered just like any other medical disease. Lack of parity is one of the key remaining barriers to overcoming stigma.

AT: What about the economics of treatment?

DC: I can't think like an economist, but I can tell you that as the most powerful country in the history of the world we ought to be made treatment available when needed. I don't know the answer to the economic part whether that should mean universal coverage, total freedom of getting any specialist you want, I don't know whether there is a need to have some barriers, but I do know that given our technology and the power and economy of our country, we could do a lot better.

AT: Do you think that the Canadian system is better?

DC: I don't know enough about it. Canada, I guess, has universal coverage, but I don't think people in Canada are that happy either, in terms of getting timely care in certain sectors. Again, I don't know things in detail, but I've heard that if you're going to need an elective operation, you have to wait a long time in Canada. Here, with the right coverage, you don't. So, maybe Canada covers more people, but to a less comprehensive degree as at least we do for some segments of the United States population.

AT: You are really focused on your research.

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- DC: Well, when you're at NIH, it's the only way to be; I see a couple patients privately, so I have a small private practice. But the bulk of what I do is to see patients in the context of participating in research. Of course, at NIH the only way to be seen in the intramural program is to be involved in research.
- AT: Can you tell us something about the clinical studies you were involved with?
- DC: I have been involved in testing new medications in clinical trials that involve placebo at some point. In general, after every protocol is over, we always treat patients for free the best we can until we can get them optimized in terms of their treatment. So if a patient wants to join a clinical trial, there might be an eight-week period where they might get placebo, but when it's over they get the best care we can provide for free as long as it takes to optimize their treatment. So that's one type of study that they could participate in. We also have imaging studies using magnetic resonance imaging and PET, and we also have family studies where we are looking at the inheritance of different diseases. In these studies the patients are involved in extensive interviews.
- AT: Do you have a large patient pool to recruit from?
- DC: No, I don't think so. You'd think there would be, because what we provide is free. In many cases it has been very difficult to recruit minorities into research because of some terrible instances in the past in terms of research abusing minorities in some way, so that there still is an element of mistrust depending on the research site. At NIH, most of the researchers and research staff are Caucasian. I think that is somewhat of a barrier for many minorities to come to NIH and participate. So in that sense, the lower socioeconomic classes of minorities don't easily come to a research setting that is primarily Caucasian, because mistrust still exists. We have responded to this problem in two ways. First, we have established a Hispanic initiative in which we have recruited Hispanic researchers, psychiatrists, and Hispanic staff, that has resulted in a lot of Hispanic folks participating in research and feeling comfortable. The second thing we have done is to develop collaboration with Howard Medical School, which is almost 100% minority run, with minority patients. We have established a relationship with them that involves giving them a grant to work with us to have our projects being run at Howard in collaboration with the staff at Howard, who are primarily African-American, so that we can break down barriers there. There are some patients who come because finances are an issue. If you have scans as part of the research, we may pay the patient. The ethics committee looks at that very carefully to make sure that the amount of money that you would pay a patient is not

coercive in some way. In general, people who volunteer for research, I think, see it as maybe a good way to get a comprehensive evaluation and so forth. So if you look at our patients, they are not in the lowest strata socioeconomically in general. They are pretty much middle class.

AT: What is the ratio between males and females?

DC: The data is clear that after puberty women are about twice as likely as men get depressed, and admit to depression, according to surveys. So if you interview a representative population of the US, then you will get twice as many women reporting symptoms of depression than men. Now, if men are not telling you about it, then that's not a true rate. That's why I'm just qualifying that it is interview based. We don't have a blood test that says no matter what you're telling me I know you're depressed. But it's probably true that women are more vulnerable to depression. Why that is we really don't know yet. Obviously, we looked at the various reproductive hormones that distinguish men and women, and around the time of childbirth, postpartum, so, we do know that changes in reproductive hormones do increase vulnerability to depression postpartum compared to other times in a woman's life. We do know that menstrual-cycle-related dysphoria is related to rapid changes in hormones. We do know also that around the time of menopause, what we call perimenopause, when there are rapid changes in female hormones, there is an increased risk for depression. So, around childbirth, during the menstrual cycle, and during the initial time of menopause, we do have a handle on what might create an increased risk for depression in women. But all the other times, when there are still higher rates in women, like when you're premenopausal and you're not delivering a baby, and you don't have a depression related to your menstrual cycle, there is still a higher rate in women, and we don't know why that is the case, at this point.

AT: Do you think the social status of women is a contributing factor to the higher proportion of woman than man with depression?

DC: I'm not aware that there are data to support that. The women who are depressed who we see are not saying, "I'm depressed because I'm not getting paid enough at work, and a man with the same skills is getting paid more, or I didn't achieve what I wanted in life because I had kids, a dual role". You see that in occasional patients, but you see these same kinds of problems in men, disappointments in life and so forth that relate to depression. But I don't think there are data to suggest that the primary reason for women having increased risk is related to social discrimination in some way.

AT: Do you think that social factors play any role?

DC: It's hard to prove a negative. I don't know how I would prove, or you would prove it. My sense is, and this is more of a guess, that it's not the primary reason. Speculation is that men and women are different in how they handling emotions, in general. That doesn't mean a particular woman is different from a particular man. But there are gender differences because men are built differently from women. So what I'm getting to is that women may have certain strengths that men do not have in terms of the regulation of emotion, and more honest with their emotions. My guess is that's not all society driven. You know, that men don't cry whereas women cry. I think that's built into the gender differences. If you look at other animal species, male animals and female animals are quite different in how they behave. It will vary with the species, but there are very clear differences in terms of roles and so forth, that were built into the organism to promote survival. So, I suspect that women have certain behavioral characteristics that have been selected for in evolution. I mean, there's a reason that women have the babies. And I'm sure that the hormones that are released at the time of childbirth are related to connecting to the baby and being a good parent and making sure that baby survives. That is particularly important in the human species where babies can't survive without parenting, or without the mother. So I suspect that in women there are a lot of positive sides of the differences in how emotion is regulated, and there's a lot more emotional health related problems in women. But there may be a flip side, and the flip side may be some increased vulnerability to depression and anxiety. There's strength and there's, in a sense, weaknesses, and that relates to gender differences. We don't have much proof of what I just said though. So that's why we must speculate that maybe the differences between men and women are not quite as large as the surveys would suggest. It might be that women are more likely to reveal depression, and men have more of a stiff upper lip and don't want to reveal that they're suffering from depression.

AT: What are your thoughts about depression in adolescence?

DC: I became interested in it from the new information that was coming out. When I was trained, we were taught that depression generally started in midlife, and that you didn't see it commonly in children. And that was wrong. So over the past, say, two decades, it has become apparent that depression can be a major problem, particularly in adolescence, but even prior to puberty. So that is in part, why I became interested in adolescent depression and began to understand, why it is, from a biological point of view, very different. We are considering one form of a disease that

might start at age 40 versus an other that you see quite early in life as a prodrome that gets more full blown at late adolescence and early adulthood. This might become a very important research question when we discover the causes of the disease and learn how to intervene early and ultimately prevent the diseases from happening.

AT: What was the evidence for the suggested high rates of depression in adolescents?

DC: The surveys. We started getting surveys by interviewing adolescents and realized that there was a high rate of depression.

AT: That they themselves were identifying?

DC: That they were identifying. Also the rates of suicide were now being catalogued, and so depending on the survey, between ages 18 and 24, or 15 and 24, suicide is the second leading cause of death in adolescents, accidents being the first. So mortality is a big problem there. My son goes to NYU. He's a freshman. In the first month of school, three kids committed suicide at NYU. Suicide is a big problem in colleges. Depression is also a huge problem in colleges that has been under recognized, under studied, and under treated. That is a vulnerable age for many things, including depression. You leave your home; and your parents are not there to monitor if something bad is going on with you such as depression. You get into a very intense peer-run environment; you're living away from home for the first time. So it's a stage of life where you are quite vulnerable and there's no oversight. The school can't be a parent to all kids, so colleges have got to figure out how to provide the right kind of support for kids when they come. The suicide rate in college is just one example that we're not doing a good enough job.

AT: So you've advocated giving medication to teenagers to help them deal with depression, and you've also said that antidepressants don't really cure this, so what is the goal then in medicating teenagers?

DC: We have a lot of work there to do regarding medication. We haven't fully clarified the role of medication in adolescents and younger children at the moment. And what I mean by that is that the older antidepressants, the tricyclic antidepressants, which clearly work in adults, don't appear to work in children or in adolescents. So those drugs were really never used in children and adolescents. Then when the SSRIs started to be looked at, particularly in adolescents, there were some positive studies with Prozac that led it to be approved for the younger age group. But, in general, it has been harder to show efficacy of the SSRIs in younger people than it is in older people. So it's a trickier decision regarding the use of medications in the younger group because the evidence is not as clear. There also may be a group of young people who are quite sensitive

to the side effects of the SSRIs. There has been a recent report in the last few months, suggesting that some of the SSRIs don't appear to work in adolescents with depression, and in a small subgroup they induce an agitated, impulsive state that can be dangerous to a young person. So the decision regarding medication is trickier, and it really gets down to the individual patient level where it's a little bit more of an art than a science. So if an adolescent comes to you and is very depressed and suicidal, you definitely will try psychotherapy, because there is some evidence that different forms of psychotherapy work. And it is a given, that you will provide whatever kind of psychosocial support, but if it doesn't work, you might then add an SSRI and carefully monitor the patient, more so than with an adult patient, for any of the side effects that I mentioned.

AT: What is your stand on testing drugs in children?

DC: It is very important. How else are we going to know if they work?

AT: What about the ethics of it?

DC: I think the ethical issue is more the opposite; if you don't study them how are you going to know if they work. Pediatricians know very well that children and adolescents are not just little adults. Their body is developing. Their brain is developing. Medications that work in adults may not work in children. Diseases that have an onset earlier in life may be different from a similar disease that starts later in life. So if we are going to effectively treat children and adolescents, we have to test the medications. The question is how to do that safely? Most of the time right now, efficacy has to be shown first in the adult population and then you move down to children. So that you've established a good safety base before you start moving down in age. But that doesn't make sense. If we find out, using the techniques we talked about earlier that early onset depression or anxiety has a different biology, and we have identified that biology, we will have a good target for novel drug development. Then there might be a case in the future, for testing a medication that has not yet even been shown to be helpful in adults. You reserve it for the most severely ill child, perhaps, where standard treatment has not worked, where we really need something else to be tried. So, there are various approaches that address the ethical issues.

AT: What do you think again about the ethical and political controversy about SSRIs and suicide in adolescents?

DC: What are my thoughts about that? There were a large number of studies with a low frequency side effect of impulsivity and aggression that increased suicidal ideation.

AT: I understand the FDA is going to conduct studies in adolescents.

DC: Yes. There may be differences among the SSRIs, because there are studies that Prozac worked versus placebo. There is some data that Sertraline might work, although it is fairly weak. So, this gets back to what I'm saying; it's not as clear cut that these medications work in adolescents. Most clinicians feel that there is definitely a group of patients in which they do work, and if you monitor carefully they are safe. I think that, as a field, and in the absence of anything else being available, we've got to be wise in how we ultimately make our decisions, so that the patients that do respond to these medications have access to them. The appropriate warnings are in place to make sure that everybody knows the limitations of the available evidence and the side effects that we've got to carefully monitor.

AT: How do parents know if toddlers, small children are depressed?

DC: I don't know how you know if a two-year-old is depressed.

AT: What about parents who just feel really uncomfortable with the idea of giving kids all this medication?

DC: That's appropriate. I mean, parents should feel that way. You should recommend medication if necessary and work with the parents in seeing that there is merit to it. But everybody should have a baseline discomfort for medicating children whose body and brain are still developing. There are circumstances where the best psychotherapy has not worked and the child looks as having bipolar disorder. Then, as a parent, I would probably say let's try some mood stabilizers because nothing else has worked. He or she is in pain. She is not functioning in school. He is not making friends. It's not an easy, but you take your available information and try to make a good clinical decision.

AT: Let me ask you something about how anxiety and depression can be viewed as separate and related illnesses?

DC: The distinction between anxiety and depression can be blurred. They are not as distinct as you might expect from looking at the diagnostic manuals. They overlap to a degree. Many patients meet criteria for both an anxiety disorder and a depressive disorder. If an individual would meet criteria for both an anxiety disorder and a depressive disorder, does that mean they are two disorders? They might just bearing manifestations of the same underlying problem. Sometimes what we call the phenotype is a little bit more anxiety than depressive symptoms, but in reality the underlying cause of the problem is similar between anxiety and depression. The distinction is a false one to a degree. There is some evidence to support the idea that there are various forms of anxiety defined in children, as for example separation anxiety and panic anxiety, and there is evidence that if you have either of them you are at greater risk for getting

depressed later in life. So if we're thinking about an underlying disease process that might first manifest as anxiety symptoms in a child and then emerges as depression later in life that is one piece of evidence that the distinction should be more blurred than it is. And, in fact, the SSRIs seem to work pretty well for anxiety in children. The available data is quite strong in comparison to treating the depressive symptoms. Secondly, there is no doubt that the SSRIs, work for both anxiety and depression. It is more scientifically accurate focus on what they do, that they block the reuptake of serotonin, for example, rather than saying that they are anti-depressant versus antianxiety drugs. Drugs that have the characteristic of blocking serotonin reuptake and increasing the amount of serotonin in the synapse have the property of being drugs that work for symptoms of sadness, depression, as well as for symptoms of anxiety. The distinction, from my point of view as a scientist, as someone who is interested in the underlying causes of the diseases has been overemphasized by the field and not necessarily by the pharmaceutical companies. This is beginning to impact on how we are going to diagnose people in the future. There have been a number of task forces that have been put together to start preparing for future ways of diagnosing patients based on the prospect that we're going to identify genes, vulnerability genes, protective genes, as well as using imaging to define abnormalities in brain circuits. So we suspect that our diagnostic system is going to look very different in the very near future. We also suspect that the distinctions between anxiety and depression will be a lot more blurred, and the way we will diagnose people will be a little bit more the way we diagnose other medical disorders. We will draw blood and look at the genes and say you have five vulnerability genes for symptoms of anxiety. We'll give a brain scan and say, you know, your hypothalamus is hyperactive, and since you are feeling depressed and anxious, we will give you the appropriate medication based on your biology.

AT: How soon do you think this will happen? What about the role of industry in this development?

DC: I think it could happen within the next decade, because of the tools that we now have that are so dramatically more efficient than we had in the past. Your last comment was about the pharmaceutical industry. All I can say is that I have not seen industry being the driver in how the field of psychiatry is making diagnoses, and how we are emphasizing one disorder or another. They've had, as far as I can tell, no impact on the way the American Psychiatric Association went about developing DSM-III, DSM-III-R, and DSM-IV. I know they've had no impact in preparing diagnostic systems. So in that sense, I don't see the impact.

Now, have they impacted on the way practitioners work? I'm sure that's true because people get "detailed" all the time. Doctors in general, not just psychiatrists, tend to use brand names rather than generic names. They do that because, I think, they're being detailed. If you look at the science, generic Prozac, fluoxetine, should sell as much as Prozac, the brand name that Lilly sells.

AT: What are your thoughts about availability of information on drugs?

DC: That I definitely believe in. You asked a number of different questions within that overall question, so let me try to address them individually. Is it true that the pharmaceutical industry should be more revealing of negative data? I guess that's one point you were trying to make. And I say, yes, definitely. And I've written an editorial about that in the journal that I edited several years ago. So I think when they have negative data that impacts on our treating of patients. So, that should definitely be out there. No question about it. Are there instances of where there has been data hidden to the detriment of patients because there was negative data, but doctors were still prescribing medication because they weren't aware of the negative data? You know, I don't know if there are, frankly. If you have specific examples, I'd be happy to comment on them. There may be examples or there may not, I'm not aware of any at the moment. But I'm definitely for more openness so that when negative trials come out we should be made aware of them.

AT: What about if information is withheld?

DC: Let me just respond to that. If that's true, that is actually a legal question. The FDA has rules on revealing that information to them, so if a company has side effect as part of their clinical trials, as Galaxo Smith Kline had for Paxil, they have let the FDA know that information. If they didn't do that, that's a legal question. So, we'll see what happens. If they did the wrong thing, shame on them. Let me address the comment I made about they doing more good than bad. The American pharmaceutical industry - actually I used to do a lot of consulting, I don't do it nearly as much anymore - drives discovery of new medications. So if you eliminated the American pharmaceutical industry, we'd be in big trouble in terms of not only just treatment of psychiatric disorders, but treatment of medical diseases in general. The NIH, the National Institute of Health can't do that. Our budget is about 28 billion dollars. If you add up all the R&D of the major pharmaceutical companies, it is an order of magnitude more than that. And they only are focusing on drug discovery. The NIH does, you know, basic research looking for disease causation, and so forth. Unless the United States government was willing to make a budget roughly the size of the department of defense, which I think is about 500 billion, NIH

couldn't do it. The government could not take over the discovery of new medications. So we wouldn't have any new drugs; it would just stop. So they do a lot of good. People can argue about, you know, that they are charging too much, that they are not revealing the data in a timely way, that they are they advertising too much. I mean, those are all important questions, but people have to recognize that without them, we would be in big trouble. The government cannot take drug development over.

AT: You have talked about some exciting possibilities for the treatment of depression and anxiety on the horizon. To what extent are these new drugs or possibilities for drugs really viable?

DC: Recently, *Science* had an issue on depression and the brain, and I was quoted: "If the CRH antagonists don't work, a lot of researchers are going to be depressed", because we are looking for new classes of medication beyond the SSRIs. There's a large body of preclinical and some clinical evidence indicating that patients with anxiety and depression type disorders have a dysfunction of CRH - corticotrophin- releasing hormones - which is a neuropeptide in the brain that seems to have anxiogenic or depressogenic properties. That leads to the hypothesis that if you block the effects of CRH you would have an antidepressant/antianxiety medication. There are a number of pharmaceutical companies that are working very hard to develop such compounds. They do have compounds that have passed animal toxicology and are in early phases of human testing. So we should know within the next three or four years, whether or not this would represent a new class of antianxiety/ antidepressant type medication.

AT: Do you think that will happen in our life time?

DC: Yes, I think so, definitely in your lifetime; hopefully in my life time.

AT: What do you consider your most important contribution?

DC: I think I've made important contributions to understanding the biologic causes of some anxiety disorders, particularly panic disorder, especially the role of norepinephrine or adrenaline in it. Our group made major contributions there. In the last decade, we have been among the leading groups in understanding post-traumatic stress disorder, which is a very common disorder, particularly in women. The implication is that psychological stress can change the structure and function of the brain. We've made important contributions to that notion and are testing that hypothesis rather dramatically. We've conducted important clinical trials that I think have had an impact. We identified the ability of lithium to help patients with refractory depression. I was involved in the discovery of clonidine for opiate withdrawal. The work in depression recently has been exciting, clarifying the role of serotonin and serotonin-related genes

in depression, identifying the neuro-circuits of these disorders. So I think I've had a strong impact across these conditions in terms of identifying biology and new treatments. More recently we've added onto that the notion of human resilience and the biology of human resilience in the face of extreme stress. I'm pretty confident that we're going to make a major contribution to that field. Most researchers focus on what goes wrong, what's the vulnerability. The psychology field has been very interested in the psychological basis of resilience, but we haven't looked at how that relates to the brain and our genes and so forth, and what makes ordinary people do extraordinary things in the face of stress. So that's an area that we are placing a fair amount of emphasis on now.

AT: Do you feel that the ascendancy of biological psychiatry has advanced the field?

DC: Yes, definitely. You see it all the time now. You know, we were talking about adolescents revealing that they're struggling with something and they don't mind being evaluated for it, and they're trying to get the best treatment. That has been very gratifying. It has been a sea change. And there are many things that go into it. The role of biological psychiatry is important, the role of prominent people being role models is very important, having it be on TV is important, whether it be the advertisements that we were talking about or it being portrayed in positive ways on TV, shows or in movies, all that helps. So doing what I can with the advocacy groups to get the word out, to support their mission, to break down stigma, is one of the most enjoyable things that I do. The ACNP is more of a scientific organization, so in that sense we work to help the advocacy organizations do their job by providing advice to them, by giving our opinions about the important issues of the day that relate to treatment. But I also like being directly involved with the advocacy groups themselves by being the chair of the scientific boards of the two major advocacy organizations in the field of anxiety and depression, the Anxiety Disorder Association of America, and the Depression and Bipolar Support Alliance, and that's been great, very gratifying.

AT: How soon do you expect major advances in diagnostics?

DC: I tend to be an optimistic person, but I would say, let's say, 15 years. Ten feels a little too short, 20 too long. So in 15 years, I think our diagnostic system will be radically different. We will have genetic profiles that will enable us to begin to quantify risks and resilience to the effects of stress on our functioning psychologically. We'll know genes that relate to risk and resilience to depression and anxiety. So I'm pretty confident in 15 years we'll have a set of genes that we can look at by drawing your blood. I'm confident that our imaging techniques will tell us how those genes will

affect parts of your brain. And then, most importantly, we'll have a much better understanding of how your environment interacts with what you're dealt with genetically. And that will help us devise ways of raising our children, structuring our own environment, by knowing where our risks are and where our strengths are in a more precise way, that we'll be able to do a much better job of prevention. One way or the other within the next 15 years we will have new medications. I'm hopeful there will be a couple of different new classes of medications that are more potent and more effective than the SSRIs. So I'd say better than 50/50 that those kinds of things will occur in about 15 years.

AT: It is the opinion of many that depression is one of the most disabling illnesses?

DC: The statement that it is among the most disabling illnesses is not an opinion, it's a fact. So, for example, the World Health Organization conducted research that has looked at a whole range of diseases, the full spectrum, essentially, of medical diseases, and their impact on morbidity, mortality, functioning in terms of social and work environments, and depression came out among the most disabling. Depending on how you cut the pie, depression is in the top two or three most disabling of all illnesses along with coronary vascular disease. Those generally are the top two no matter how you analyze the data. This is particularly true in western countries, because the problems with infectious disease are much greater in less developed countries where they don't have antibiotics available. So why is that? It starts early in life as we talked about it. It can be chronic in many patients. It can result in suicide; in certain age groups suicide is among the most common causes of death. It co-travels with other medical diseases and influences their development and their prognosis. So, for example, there are recent data that depression increases your risk for getting heart disease and for getting Alzheimer's. These are two examples. There are very clear data that if you have depression and you've had a heart attack, your risk of dying from heart disease is several-fold greater. There is an interaction between the biology of depression and the biology of coronary vascular disease that increases your risk. If you have diabetes and you are depressed, the ability to control your diabetes with insulin and other medications is impaired. There is an interaction with the biology of depression increasing hormones like cortisol, which affects the body's response to insulin that results in depression worsening your prognosis of diabetes if you don't get treatment. There are many other examples, but those are just a couple that indicates that the co-traveling of depression with other medical diseases increases their impact, making it among the most serious of all diseases.

AT: Is there anything we left out and you would like to add?

DC: No, I think you've done a good job asking questions, covered a lot of ground. What I would be interested in, you know, as a result of your project, is what role history can play in understanding our field? It's my understanding that if your history is correct you're supposed to not repeat that is bad. So if there are things that you uncover as a historian in looking at the field of psychopharmacology that would be good advice for avoiding, on one hand, or if you've identified things that worked out well so we should emphasize it in the future, I'd appreciate hearing about it.

AT: We have to leave that for another occasion. Thank you very much.

DC: You're welcome.

JOSEPH T. COYLE

Interviewed by William E. Bunney, Jr.
Boca Raton, Florida, December 11, 2007

WB: I'm William Bunney, and I am interviewing Joe Coyle.* It is December 22, 2007 and this is the 46th meeting of the ACNP in Boca Raton, Florida. First question is: where were you born?

JC: I was born in Chicago, Illinois.

WB: And, tell me a little bit about your education.

JC: Okay, my father was a physician in Chicago and my mother was a nurse. I had two older sisters and grew up on the south side of Chicago. I went to a Jesuit high school, where I studied Latin, Greek and French and went off to Holy Cross College in Worcester, Massachusetts, which was a Jesuit college.

WB: Do you know Hebrew?

JC: Actually, my roommate was taking Hebrew and I ended up being a French and Philosophy major. I did my required science courses mostly in the summer school and had the good fortune to spend my junior year living in Paris, which was really a life-altering event.

WB: How was that?

JC: Well, I grew up in parochial schools with a big P and a small p and so at Holy Cross we went to Mass every morning and we had to have lights out by eleven o'clock. Then suddenly I was dropped into Paris where there were no rules and it was a very different culture. It was a time when students were starting to organize.

WB: Now, where was this in your education?

JC: This is 1963-64.

WB: And, this was College?

JC: College. I was there in 1963 when Kennedy was assassinated, which was very striking, because the city, the Nation, France just shut down for his mourning. And, you could really see how much impact he had on the world. So anyway, I applied to medical school and I remember I was interviewed at Hopkins and they asked me if I had done any research. And, I said, oh yes, I did a lot of research on Samuel Beckett. But, anyway, I ultimately was accepted at Hopkins and I went there with the plan of being a psychiatrist. I had read a lot of Freud and Lacan and was very interested in psychoanalytic thought and existential philosophy. In my sophomore year, I was taking a pharmacology course and there was this

* Joseph T. Coyle was born in Chicago, Illinois in 1943.

psychiatric resident named Sol Snyder, who was teaching a new section in the course called psychopharmacology.

WB: Now we are at Hopkins?

JC: Yes, we are at Hopkins and he was a faculty member in the Department of Pharmacology and he was, I think, a second year resident in psychiatry. The lectures were just really exciting. It was a whole new way of thinking about the brain and behavior, LSD, stimulants, antipsychotics, antidepressants and he would sit on a tall stool with a big jug of water and would give his lectures. And we all fantasized that it was a jug of martinis, of course.

WB: What was the year of this?

JC: So this would be 1967. I went to see him and said, you know, I'd really like to spend some time doing research in your laboratory. Of course, he was interested in as many hands as he could get and he said, sure. So, the first quarter in my junior year was a free quarter. He did something, I think, very, very special. He really allowed you to do your own research, design experiments. So, within two weeks I was immersed in this whole process of discovery. And, I did bring one thing to the lab, because I had a project in biochemistry and I had read about these things called synaptosomes. Sol was studying neurotransmitter uptake using a McIlwain tissue chopper to chop up the tissues. The problem with that is that the tissue settles out of solution in the pipette. I suggested that we work with synaptosome. We did and, of course, it's like milk and you'd get very accurate pipette results. So, that was my introduction to research. And during the period of time that I worked in the laboratory I was able to identify that the dopamine transporter was different from the norepinephrine transporter and that was published in *Science*.

WB: Was that your first paper?

JC: That was my second paper.

WB: What was your first paper?

JC: My first paper was in the *Journal of Pharmacology and Experimental Therapeutics* on characterizing norepinephrine uptake in the synaptosome preparation.

WB: You started off with a bang.

JC: So in my junior year I had an elective or free quarter when I worked in Sol's laboratory, and then I did my mandatory medical, surgical rotations and pediatric rotations. In senior year, you were supposed to redo surgery and medicine rotations. That seemed kind of silly and I wanted to do more research and so I was a special case that they put forward to the Dean to see if I could take more elective time. Ultimately that resulted in the rules changing at Hopkins, allowing more elective time for the medical

students. I graduated and did a pediatric internship and I was interested in ultimately doing child psychiatry.

WB: And where was that?

JC: At Hopkins.

WB: At Hopkins, too, yes.

JC: Right. I interviewed for positions down at NIH and I should point out that medical school was a bit of a struggle for me, especially the first two years, because I had such a light science background. When I went to interview for NIH, I interviewed with Floyd Bloom, Erminio Costa, and Julie Axelrod. I will never forget my interview with Erminio Costa. I go in and sit down and he looks at my transcript. I'd never seen my transcript. Hopkins never told us what our grades were. He looks at my transcript and says, "What are you doing here?" And I said, "What do you mean?" And he said, "These grades, these grades are terrible!" I replied, "Well, you invited me". Anyway, I had the good fortune of being accepted into Julie's lab and, so, I went right after my internship and spent three years in his laboratory. The first year was 1970. It was the year that he won the Noble Prize, which was very exciting.

WB: So, there was no residency there?

JC: No. Well, what happened was I was planning to do residency, but Julie had a slot open and said, I can't guarantee I'll have a slot in three years. Since I watch news at night and I wasn't interested in going over to Vietnam, I said, "Okay let's do it". So, I spent three years in his laboratory and it was just great; you know, every morning when you wake up, you are all charged up to go to the lab.

WB: Can't wait to go to work.

JC: Julie was an incredible mentor and he pretty much let us do what we wanted to do as long as it was within the broad theme of the laboratory. I wanted to study the development of the catecholaminergic system in the brain; there was nothing published at the time on neurotransmitter development at all. And, that was fine with him. Ultimately, several of the papers I published, he said, I really didn't have much to do with that, so you don't have to put my name on the paper. That was the kind of person he was. His desk was right next to the scale and everybody would have to weigh out their reagents everyday. So, everybody would go by and there would be Julie reading papers and every once in a while he would say, come over here and tell me what you're doing. And, then, you'd review the data with him and he'd make suggestions. So, it was a very light handed type of supervision. But he did other things that I think were extremely important. He'd obviously get a lot of papers to review. He'd give these papers to the post docs and then he'd go over

our reviews and make constructive criticism. Pretty soon we'd be getting the request directly from the journal, so he was creating some visibility for us. Sometimes he'd not be able to give a lecture and he'd send one of us in his place and, so, he really taught you, not only how to think about science, but how to be a scientist and how to develop yourself as a scientist. So, that was an extraordinary experience.

WB: How did you view his thought processes, his scientific thought processes?

JC: Well, you know...

WB: Nobel Laureates` often have a unique way of viewing the world. How would you characterize his?

JC: Well, one of the things he taught us was that in ninety nine percent of the experiments that you do, you know what the results going to be; and that the one percent, when you get completely unexpected results that's the most important one. You need to redo it and make sure, in fact, that that is the outcome, and, then, there is a sort of head scratching thing. And that's where you can get some very interesting insights, because then you're going out in a way that other people aren't thinking about. He would always say, "Be there firstest with the mostest".

WB: Which meant what?

JC: Well, it meant get into an area that isn't crowded and, then, really flesh it out. I found that very helpful. I've tended to work in areas that aren't very heavily populated; sometimes you can get burned with it because you can be too far ahead of the curve. For example, one of the very hot animal models now for schizophrenia is the methylazoxymethanolacetate or MAM lesion model. We published on the MAM lesion in *Science* thirty years ago and couldn't get an NIH grant funded for it in schizophrenia, because everybody believed back then that schizophrenia was a functional disorder and didn't result in structural changes in the brain. I went after that, because nobody was doing it. It seemed important to me and that's the way Julie would do it.

WB: So key mentors that you had were Sol and Julie. Were there other people, other key mentors?

JC: Well, sort of an academic mentor was Guy McKahn, who was the head of Neurology at Hopkins, He was out of my specialty, but he knew about the brain and he was very helpful in thinking about making academic decisions.

WB: So, you've talked about your first project, but has there been a central theme throughout your research?

JC: Well, another thing Julie would say is that you follow the result; that's what guides you. And, so, I got into glutamate 32 years ago and had the *Nature* paper with Robbie Schwarcz, my first post doc when we injected kainic

acid into the striatum and reproduced the pathology of Huntington's disease. That suggested to me that, at a time when many scientists didn't believe that glutamate was neurotransmitter, that this could be a very important transmitter. So, glutamate has been a theme of my life for the last thirty years, one way or another. I did a lot on neurodegeneration. I've been working on glutamate and schizophrenia for over a decade, so that's been a major interest. I did a lot of developmental work from the 1970s to probably the mid-1980s, and then moved on from that.

WB: Are there technological developments that came along with this?

JC: Well, one of the things I learned from Sol is to keep it real simple; find a simple assay and really milk it for what you can get. And, I'm not saying that in a cynical way; it can be very efficient. So, one of the exciting things about science is that it's not like being on the Ford assembly line. You're not doing the same thing every day. What I've enjoyed about my career is that we've done a lot of different things. I mean, I started out classical enzymology and I got to immunocytochemistry; and ligand binding and then molecular biology came along. We are kind of like sharks; if we don't keep moving, we are going to die. And, for me, that's been a challenge. It's been exciting to find new ways of thinking about brain.

WB: Almost the renaissance. Okay, financial support?

JC: We've lived through the generosity of our citizens, through the funding to NIH; although, there have occasionally been some lean times. I've been continuously funded since I started my career and feel very lucky to be funded now. I know how difficult it is for many good people to get grants. I think we live in very perilous times right now for science. NIH and NARSAD have been generous over the years.

WB: And, what would you say as your major findings were?

JC: Major findings? Well, a couple of different things. When I was doing developmental research we were able to show that aminergic systems are among the earliest to be formed in the brain. I think that now it's plain and clear that these systems play a major role in regulating brain development. We sort of predicted that, but we didn't have the tools to really answer that question in the 1970s. Second major finding was the kainic acid lesion and people are still thinking about "excitotoxicity" in Huntington's disease. And, you know, we predicted back then that glutamate might be important for neurodegenerative processes.

WB: Were you one of the first to say that?

JC: Well, I have to give some credit to John Olney. He was the first to really define "excitotoxicity." But all his work had been done by administering glutamate in the periphery, and in the areas of the brain where the blood brain barrier was deficient would there be neural degeneration. Where we

made, I think a strategic advance, was to take potent glutamate receptor agonists and inject them so you could make predictable lesions in specific regions of the brain. And, we used that technique to lesion the nucleus basalis and showed that this reproduced the cholinergic deficits of Alzheimer's disease.

WB: Have you made that landmark finding of glutamate neurotoxicity?.

JC: Well, we did. I looked at ISI and we are pretty heavily cited; we are up to forty thousand citations so far.

WB: Well, that's impressive.

JC: Until memantin (Namenda) came along, the only treatments available for Alzheimer's disease were directed at reversing the cholinergic deficits and, though they may not be the greatest, they certainly help some people.

WB: Right, right.

JC: And, then, more recently, we've been working on this hypothesis of NMDA receptor hypofunction as being the proximate cause of the pathophysiology of schizophrenia and I think at this meeting it's very evident that we now have a pathologic circuit in schizophrenia that makes a good deal of sense. We actually predicted that in a paper we put out in nineteen ninety-six. It was the working hypothesis for our research program on schizophrenia. We applied four times for a NIMH center grant on schizophrenia and got it on the fourth time. Again we were a little bit ahead of the time then, but it certainly has worked out quite nicely, I think. When I was running this schizophrenia clinic at Hopkins, Sol came up with the dopamine hypothesis, extending Arvid Carlsson's work. We were doing dopamine radioreceptor assays to measure neuroleptics in blood to optimize treatment. At the end of the day it was very discouraging, because we thought we knew what was going on with the disorder, but those patients were still profoundly disabled. Now, it is extremely gratifying that we may be able to get a handle on this very disabling disorder.

WB: So, what are the targets you see now for future drug developments?

JC: Already we have this very wondrous finding by Lilly that their mGluR2/3 agonist tracks right on with olanzapine in terms of antipsychotic efficacy. It would be acting at the down-stream disinhibited glutaminergic pyramidal neurons that are driving subcortical dopamine release. As David Lewis has pointed out, the hypofunction of NMDA receptors is specifically on the GABAergic interneuron, so they end up being hypofunctional. As we've shown at this meeting, when you knock out serine-racemase so there's no D-serine, which reduces NMDA receptor function, you get the reduction in GAD67 and the reduction in parvalbumin that is the neuropathologic signature of schizophrenia. So, as David has pointed out,

another target would be the postsynaptic GABA-A receptors. Certainly, a third target would be more proximal, which would be anything that would enhance NMDA receptor function via the glycine modulatory site, like glycine uptake inhibitors. We actually published ten years ago the first report on glycine uptake inhibitors enhancing LTP and NMDA receptor function. I know a number of companies are looking at that site now. And, we've also used D-serine, itself, which is a potential treatment.

WB: Who are some of the other people in the field that are working in the area that you are working in?

JC: Well, there are a number of people and, of course, I think we all like to point out that I did this, or I did that, but it's really based on findings of many other people. David Lewis and Francine Benes, in their post mortem neural chemical studies, I think, have been extremely important. I mean, back ten years ago, you really did feel like the blind people and the elephant, because there was a finding here and a finding there but it was not coherent. Now these findings on the GABAergic interneurons have been highly replicated, so I think their contributions have been extremely important.

WB: Are there others?

JC: You.

WB: Okay, others?

JC: Well, you know, some of the imaging work like Marc Laruelle's has been very important. What has also helped us immensely are the results from the genetic studies that are coming out, that several putative risk genes are clearly involved in neurotransmission and several of them are within two degrees of separation from the NMDA receptors..

WB: Do you see patients now?

JC: No, I don't. When I became the Chairman at Harvard, my schedule was so chaotic that it was difficult to maintain a practice.

WB: Before that, did you?

JC: Oh yes, when I was Head of Child Psychiatry at Hopkins I had a substantial group of patients that I followed. They grew up with me, so to speak, kids with serious mental illness, autism. And I would attend two months of the year our inpatient units. I miss that part of my life.

WB: Let's just go through your career, because we sort of skipped around. So you were with Sol and then...

JC: I went to Julie's lab and...

WB: ...when you left Julie's lab?

JC: Julie let me stay a third year, so I spent three years in Julie's lab and, then, I started to look for residencies. Sol had worked out this deal to do residency and be on the faculty in the Department of Pharmacology and,

so, there were two places I was looking at, one was MGH with Seymour Kety and the other was Hopkins. At Hopkins they said I could start on the Pharmacology faculty in my second year of residency and also with my laboratory, and Seymour Kety said, well, we don't do that at Harvard, and I said, well, gee, I'm sorry, and, so, I went to Hopkins. Seymour wouldn't talk to me or recognize me for about fifteen years. Then we got to be good friends.

WB: Were you happy with Hopkins?

JC: Hopkins was just an extraordinary place at that time. Departments weren't barriers. Neuroscience was just taking off. So, I was collaborating with Mark Molliver in Anatomy, Mahlon DeLong in Neurology, Don Price in Neuropathology and it was great fun. It was great fun and we accomplished a lot. So, anyway, I started on the faculty and I got my first grant in my third year of residency. I got the grant; it was for twenty-four thousand dollars. Twenty four thousand dollars went a long way back then, so I was able to set up my lab. The first person that I hired was Rob Zaczek as a technician. Rob is a dear friend of mine. He's running neuroscience at BMS now. My first post doc was Robbie Schwarcz, who sold his stamp collection to come over and do the post doc. That was a very productive relationship and he's a dear friend. And, then the lab grew, got more grants, had a developmental project going and had the neurodegeneration project going. And also I had an Alzheimer's project funded; so we were running on 3 RO1s.

WB: How many people in the lab?

JC: Through the 1980s - I left in 1991 - I would say we had over a dozen people. I really didn't believe in professional technicians, so we would get students, who just graduated from college, who were uncertain whether they wanted to go to graduate school or medical school and they'd come work in the lab. We had those, and everyone, except one, either went to graduate school or went to medical school. Some of them are successful scientists now. For example, I ran into Paul Schlesinger recently. He was a technician with me and now he's on the faculty at the Salk Institute.

WB: So, you moved up to become Professor there.

JC: Right. I finished my residency in seventy-six and was made a professor in nineteen-eighty. And, another interesting part was, that I didn't do my training in child psychiatry because by the time I got done with my residency my lab was going. Anyway, I looked around and I couldn't see any place that I'd want to go to be trained in child psychiatry. The programs were very much psychoanalytic and there was very little being done in terms of brain development. So, after Leon Eisenberg left as head of child psychiatry at Hopkins, they tried to recruit a number of

people without success. Paul McHugh pulled me aside one day and he said, "What do you think about becoming the head of child psychiatry?" I said, "Geez, I hadn't thought of that". I had to go to a conference up in New England. It was in the middle of the airline strike and I took a train. So, I had all the time to think about it. I decided to take the position considering that, maybe we could have a new way of thinking about child psychiatry with our developmental brain research and and bought a textbook of child psychiatry and was able to set up a division populated with people that could teach me what I thought I needed to know and teach our residents what they needed to know about child psychiatry.

WB: I never heard that one before.

JC: So, I recruited Randy Blakely. He was getting his PhD in Neuroscience. Randy is doing great stuff on serotonin transporters in autism. I recruited Joe Pivin, and now he is a Professor at UNC and runs their mental retardation center. I got Alan Reiss, and he's Head of child Psychiatry at Stanford, doing great research on fragile X in autism. And, I also recruited Paramjit Joshi, who is now the Head of Child Psychiatry at Children's Hospital in DC.

WB: Were these all the people you hired?

JC: Yes.

WB: That's a nice legacy, too.

JC: Yes, I'm proud of that.

WB: Tell me a little bit about your teaching experience.

JC: Well, I thoroughly enjoyed teaching and when I was at Hopkins, I had faculty appointments in Pharmacology, Neuroscience, Psychiatry, Pediatrics, and over in the School of Public Health in Toxicology. I would teach in all those programs. So, I taught several of the lecturers in neuropharmacology in the pharmacology course and several lecturers in neuroscience course, taught the medical students in psychiatry and worked with the residents and taught them. I really did enjoy that.

WB: In 1991 you moved to Harvard. Why did you move?

JC: When I had come in to take over the Division of Child Psychiatry at Hopkins, it had 3 FMG faculty members and no research. And, after eight years, I had built it up, so we had two thirteen-bed in-patient units and we had a faculty of about a dozen. Most of these faculty members were involved in research. We had grown to a several million dollar research budget in the Division. But, then, the Head of the Hopkins Hospital had set up his own HMO. Medicaid was paying the hospital ninety-eight cents on the dollar for our beds and they were paying us five dollars a day to take care of the patients. So, my Division of Child Psychiatry was starting to go into the red, big time. This HMO would refer the patients to the

emergency room where we evaluated them and then, send them to a little hospital that they had developed in a Victorian house and they wouldn't pay us for the evaluations done in the emergency room. So, I really was getting annoyed and there was no way to solve the budget problem. I talked to the hospital administrator, who responded that if you're a good business man, you can solve this. He said, "People in surgery are doing fine. What are you complaining about"? And, then, Dan Tosteson, who was the Dean at Harvard, approached me. He approached me once before to become the head of MGH and McLean Hospital. I went up there and I saw this sort of tower of Babel, which was Harvard Psychiatry with all these different competing groups. So, he came back to me and said, "Look, I can put together a deal where you'd be the academic head of six of the nine programs". And he got the hospitals to commit the money to run the academic programs and it was a pretty substantial offer. I figured that if I did it right, then the other three hospitals would join. Indeed, in about eighteen months, the rest of them joined and this was known as a Consolidated Department of Psychiatry. We got a lawyer to look at this structure and it became clear that I could not deal with clinical services, because we controlled over thirty percent of the clinical services in eastern Massachusetts. That was great, because I was not interested in the business of psychiatry. I was interested in the research and the academic components.

WB: Right.

JC: When I got there, there was no grant that transcended any department and I think the total amount of NIH funding was around fifteen million dollars. MGH psychiatry had less than a million dollars worth of grant funding. Over the years we got center grants, training grants and, after ten years, we went up to around seventy million dollars for the entire research operation in Harvard psychiatry. And, I was able to condense the adult residencies so that we had three adult residencies with one application. These programs were differentiated. By and large, that worked out. There were six child residencies, and we turned them into three training sites with one core curriculum. The child residencies then became, I think, fairly competitive. So, I was pretty satisfied.

WB: This was your PhD in Administration that you got the same way you did your child psychiatry. It sounds like you transformed the whole place, in terms of academics.

JC: Right, and, then, two things happened. Dean Tosteson, I think in about 1996, had gotten together the heads of the hospitals and said, look, we've got to do something; this managed care is going to come in and it's going to be disastrous if we don't work together. His idea was that Harvard

Medical School should take academic ownership of the clinical departments and as usual, psychiatry should be was one of the first experiments. Then, he woke up one morning and read in the Boston Globe that Massachusetts General Hospital and the Brigham Woman's were merging to form this entity, called Partners. I think that was a very difficult thing for him and he had also developed Parkinson's disease. So, he stepped down. The new dean who came in I think was really much more interested in having Harvard Medical School work like it did before where the Hospitals took the responsibility for the Clinical Departments. So, I had a ten-year commitment and I got done with it and I said, I'm going back to the lab and that was a good decision.

WB: Just to backtrack for a minute, do you remember your first presentation?

JC: Yes, I do remember my first presentation. Neuroscience started in nineteen-seventy and. back then, the really big meeting for people like me was the American Society for Pharmacology and Experimental Therapeutics. My first presentation was in Atlantic City at the ASPET meeting and it was the last talk on the last day of the meeting and I'll never forget that.. It was in a room with about three thousand empty chairs, a projectionist and me.

WB: Really?

JC: Yes.

WB: Okay, what are your most important contributions to the field?

JC: Oh.

WB: You can name a couple

JC: Well, I think certainly one was the whole excitotoxic story in terms in defining true glutamate receptors and their sub-types. I would say that would be one. I would say a second one, working out this pathologic circuit in schizophrenia, I see that was important. And the third, I guess, would be the cholinergic deficits in Alzheimer's disease. We didn't discover them. Those were discovered in post-mortem studies, but what we were able to do was to work out the anatomy of the cholinergic deficits and that allowed animal models to be developed. And, the last thing, I would say, is the trainees. I mean, I've really been blessed with extraordinary students and post docs and they carry on the legacy. I'm proud of Randy Blakely, who won the Efron award. So he's third generation: Sol, me and, then, Randy. So many others whom I've trained in the lab have gone on to do really good things in science and in medicine.

WB: How may publications you have, ballpark?

JC: It's over five hundred.

WB: Five hundred. And books?

JC: I think it's seven or eight.

WB: Seven or eight books, are these edited or written?

JC: These are edited.

WB: Honors and awards?

JC: I won the John Jacob Abel Award from ASPET, which was, in my mind, a great honor. I won the A.E. Bennett Research Award from the Society of Biological Psychiatry and the Foundation Fund Award from the APA for research. I was elected Fellow of the American Academy of Arts and Sciences, a Member of the Institute of Medicine and a Fellow of the American Association for the Advancement of Science.

WB: Why don't you comment on what you do in editing journals?

JC: In 2001, Cathy DeAngelis, the editor of *JAMA*, approached me to take over from Jack Barchas as the Editor of the Archives of General Psychiatry. I've been on the editorial boards for a number of scientific journals. The Archives has always been the lead journal in the field, as far as I was concerned, and Danny Freedman was the Editor for a very long time. Danny was a kind of a mentor to me. I had been on NIH study sections with him, and he was just a really neat guy. I was on the editorial board with him. As someone who is probably associated more with basic neuroscience than clinical neuroscience, it seemed to me that Psychiatry was moving into a new realm in terms of understanding psychiatric illness and, so, I was very intrigued about the opportunity to become the editor of the Archives, both in terms of its traditions and in terms of where I think the science may be taking us.

WB: Roles in the ACNP?

JC: I've been on council and I served as a President in 2001. I served on a number of committees; most recently, the Publication Committee with Sam Enna and I think we've been able to make some important changes in terms of the Journal. Hopefully, we will be able to develop a much more robust website and moving from *Generations of Progress* to the new *Annual Review of Neuropsychopharmacology*.

WB: Was that your initiative?

JC: Yes. I chaired the committee that selected Nature Publishing Group to be the publisher of the *Journal of Neuropsychopharmacology*. Then, when we developed this Review of Neuropsychopharmacology concept, they came in with a gang-buster proposal, so they are publishing that. I think that was very good, because we are now up to a several hundred thousand dollars in income from our publications.

WB: Have you been involved in other professional organizations?

JC: I've been also very much involved in Society for Neuroscience, almost from its beginning. I served on council. I was elected Treasurer and I was elected President for 1991-92. I was able to get an NIMH minority

training grant funded through the Society when I was President. I served as a Deputy Director of that for over ten years. Joanne Berger-Sweeney, who got her PhD with me and is now an Associate Dean at Wellesley, was the PI on the grant. At the end, we were having Hispanics and African-Americans in MD-PhD programs at Stanford and Harvard. You could see that something had happened over a decade and I think we were a part of that something that created a situation where we are going to have minority members that will be very prominent in the neuroscience community.

WB: Weren't you the only psychiatrist that was ever President of Society of Neuroscience?

JC: I think I was the only practicing psychiatrist; Eric Kandell and Sol Snyder were also Presidents. At the time I was President I was the Head of Child Psychiatry at Hopkins, seeing patients and doing research.

WB: Okay, would you say something about your family

JC: When I studied in Paris for junior year in college, in the group was a gal that came from Washington DC. When I was in medical school in Baltimore at Hopkins, she invited me down to DC for a party at her house and I met this incredibly vivacious and attractive woman, Genevieve. She was living in New York, so I was kind of bummed out about that. Then, a year later, I went to another one of these parties and she was there. I thought that "I'm not going to miss on this one", so I took her up to Baltimore and fed her crabs and, so, we started a relationship and I just knew that she was the one. I don't think she was quite as convinced.

WB: You convinced her.

JC: Yes, right. I was persistent. So, we married in between my junior and senior year of medical school. She had a degree in social work and, so we got by financially and it was great. Then I went to NIH and she was working and I was getting paid. One of the problems that we confronted was, we weren't making babies and, so, we decided that we would adopt and we just let everybody know that we were interested in adopting. Another physician, who had been with my dad in the Army and they had remained friends out in the Midwest, said that he had a young girl who wanted to put up her baby for adoption, so we went out and we were there right on the day the baby was born. That was our first son, Peter, and it happened at my last year at NIH. In the lab was a PhD scientist from Vietnam. About six weeks after we had adopted Peter, she approached me and said, "I heard you are interested in adopting". Well, we just adopted a son, and she said, "my sister is head of Obstetrics in Saigon and she just delivered an AmerAsian boy, who is going to be in an orphanage". So, I remember driving that night with Genevieve and I said, you know, you don't want to have an only child, right? So, the next day I called and said we'll do

it. Well, it turned out to be very, very complicated. The Vietnamese did not want boys to get out of the country, because they could be future soldiers. We went through a period of almost two years of trying to get Andrew out. We sent money to the orphanage. The Nun would write us notes about how Andrew was doing and sent a couple of pictures. I don't know if you remember, but five months before Vietnam fell, they started to evacuate the orphans. A plane crashed and a number of orphans were killed. But things started to move and we got a call from a social worker, who was flying out with 5 or 6 orphans, among them, Andrew. And, so, that's how Andrew came to join us at the age of two. When Peter and Andrew were about three and a half, we decided for the first time to have a babysitter take care of them for a long weekend and we'd go to southern Maryland and enjoy ourselves. We went to this great Inn and I ordered oysters Rockefeller. Genevieve took one look at them and starting throwing up and she just threw up the whole weekend. That's when we discovered that David was on the way. He was our third son. They are adults now, and they've been great. Peter manages a bookstore in Somerville, Mass. He's married to a very lovely lady, who is in academic publishing. Andrew is in his third year of medical school at Tulane and is interested in International Health, The youngest one, David, is married and lives in Baltimore where he also works in publishing.

WB: Sounds like a success.

JC: Yes, everybody is healthy.

WB: Could you say something about what you are currently doing, your current research?

JC: I am the PI on a Silvio Conte Translational Research Center in Schizophrenia. The focus of the center has been on the NMDA receptor hypofunction hypothesis. Neuroanatomically, we have focused on the hippocampus. It's really exciting, because it goes all the way from molecular modeling that we do through electrophysiology with John Lisman, who is a hippocampus electrophysiologist, Howard Eichenbaum, who is very elegant on memory tasks and behavior, through brain imaging with Debbye Yurgelun-Todd and to clinical trials with Dan Javitt and Don Goff. What we have been focusing on in my laboratory is making conditional knock outs of genes that encode proteins that modulate NMDA receptor function. And, in our most recent observation we have shown that when you knock out serine racemase, there is no D-serine made and that seems to be the important co-agonist for the NMDA receptor in the cortical limbic regions of the brain. This is consistent with these risk genes that are associated with reduced availability of D-serine in schizophrenia. And, you know, your most recent finding is often your most exciting finding.

WB: It is a structural model.

JC: No, if you block NMDA receptors with, say, MK801, you'll get down regulation of these biomarkers; it's not structural.

WB: Molecular.

JC: Yes, what we think is happening is that these GABAergic interneurons get recurrent feedback from the pyramidal cells; the NMDA receptors are sensitive because the NMDA receptor on a GABAergic interneuron accounts for forty percent of the post synaptic excitatory currents. So, we believe what happens is, that with the blockade of the NMDA receptors on these GABAergic interneurons, the pyramidal cells are disinhibited and since the GABAergic interneuron doesn't know that they down regulate these parameters. So, it's a circuit problem.

WB: Okay, we are about out of time. I've got one last question and that is: project into the future. What would you like to see happen? What is going to happen, go out five, even ten years in this field? What's your projection fantasy?

JC: Well, the first thing that I'd really like to see, and I'm hoping that science will take us there, is complete parity for mental illness and addictions with medical illness, and recognized as major contributors to medical morbidity, and that there are risk genes for them.

WB: Is that a prediction that it is going to happen or that you'd like to happen?

JC: Well, I think it's going to happen. I think we'll find that the risk genes are, say, for major depressive disorder, also have actions in the periphery and that they can account for those interesting association between depression and diabetes and heart disease.....

WB: Cardiovascular disease.

JC: Yes, cardiovascular disease. You know, the brain isn't something over here and the body is over there. So, that's first, and the second thing will be true of any area of medicine. I think psychiatry and psychopharmacology will be personalized medicine to a very substantial degree. We know that what we are looking at, sort of like shadows on the wall of Plato's cave, is what our diagnoses are all about now.

WB: And, we are going to turn around and look out into the light.

JC: Yes, we are going to look out into the light and we are going to see the way.

WB: But, we're chained. We have to break the chains, and then look out.

JC: Okay, break the chains and we'll find there will be whole new ways of categorizing disorders and that the treatments will really be much more focused on etiology, genetic ideology, but also to a certain extent, environmental contributions to that. So, I think our diagnostic entities, like schizophrenia, bipolar disorder, will get broken up into much more

discrete subtypes. And, it's going to be an interesting challenge, I think, for the pharmaceutical industry. I personally think that the day of two billion dollar blockbusters that treats all things is going to disappear and it's going to be a hundred million dollar market for this drug that's a cognitive enhancer for twenty five percent of the people that we now diagnose with schizophrenia and not for the other seventy five percent. So there's going to be some fairly radical changes, I think, that are going to drastically affect the economics of medicine and the pharmaceutical industry.

WB: Okay, anything else for the future?

JC: Anything else for the future? I was at the ethics meeting today. I think we are really going to have to come to terms in some way with the relationship between the pharmaceutical industry, NIH and drug discovery. I don't foresee the day when NIH is going to be developing drugs and I do see pharmaceutical industry as having very strong science. It is much different from what it was twenty five years ago, when serendipity ruled the world for psychopharmacology. I think we are going to have to sort out what this conflict of interest issue is really all about. How can we work together without looking like we're on the take or being manipulated? And, unless we do that, I think our ability to develop drugs effectively for Society, for our patients, is going to be limited.

WB: Okay, let me just say, I've enjoyed interviewing you. It was fun. I learned a lot of things: your incredible career. You are one of the top people in the world in this area, totally active and totally at the top of your game right now, so, anyway, absolutely great.

JC: I've enjoyed being interviewed by you. It was great fun.

KENNETH L. DAVIS

Interviewed by Stanley J. Watson
Boca Raton, Florida, December 11, 2007

SW: Good morning. I am Stanley Watson from the University of Michigan and I am here interviewing Ken Davis,* the CEO of The Mount Sinai Medical Center. Today is December 11, 2007, and we are at Boca Raton at the Annual Meeting of the ACNP. This recording is part of the International Neuropsychopharmacology Archives series and it is carried out under the agency of the American College of Neuropsychopharmacology. So, Ken, in order to get us started what I want to ask you to do is consider the things associated with your early life, perhaps, your parents and your early education exposure to intellectual research environments?

KD: I guess what you are asking me is what were those important early influences that would make me think, that I would ultimately become a psychiatrist.

SW: Or, even a researcher?

KD: Or, even a researcher. I can't put a time on it when it was of that I became fascinated with the questions around behavior, but I know it was a very early age. I can recall riding down to Florida during a winter vacation, sitting in the back seat of our car, reading Ernest Jones biography of Freud. I was thirteen or fourteen and was just fascinated with the questions of how was it possible that you could understand behavior by understanding people's backgrounds and early upbringing. At an early age, I became fascinated with the questions of psychoanalytic and psychodynamic psychotherapy. At the same time, like a lot of kids from our generation, I wanted to be a scientist and I shot off rockets, had a chemistry set and probably was fascinated with the issues of the future. You know, the future seemed so bright when we were growing up; it seemed that science would unravel so many questions and would be generally for the good. So, it was with that background when I openly made a decision that I wanted to go into medicine; it was clearly from the beginning, to be a psychiatrist and to be a research psychiatrist. I probably knew that years before I was in medical school and that would be the direction I went. But, I changed from a psychoanalytic perspective to a neurochemical perspective because of the work that I did in the summers during my undergraduate years at Yale. I was hired by the Nassau County Mental Health Board, because I understood a lot of statistics that I learned in college. My job was to crunch numbers and to find out how the local

* Kenneth L. Davis was born in New York, New York in 1947.

mental health clinics were doing; and they had a lot of data, a lot of fascinating data. Data was about the diagnosis of the patients and, then, their outcomes in terms of whether they went to a hospital or they went for repeated treatment or whether they were employed. I started this job thinking that analytic or psychodynamically based psychotherapy had a lot of important answers. But, by the time I got done crunching all the data over for two years it became apparent to me that the people who were running the clinics -who were, by and large part of the analytic movement - were producing no real benefit to all the patients that were coming to the clinics, that the hospitalizations weren't changing and the outcomes weren't any good. I, then, began to visit the clinics and became more and more distressed with, what I thought was a powerful tool, talking to make people better. And, that was about the same time that the revolution in psychopharmacology began percolating down to the level of what might have been a twenty or twenty one year old. And I began to read. I remember from my senior year in college reading a lot of papers about psychopharmacology and ECT that I was slowly coming to realize that if you didn't understand the chemistry and the biology of the brain, we are never going to make these people better.

SW: So, tell me did your family have an academic, intellectual, scientific background?

KD: My mother went to about a year or two to college and, then, she was a secretary bookkeeper, and my father was an accountant. The closest that anyone came to an academic, intellectual, scientific background was a dentist in my family. My uncle was a very smart man, of whom we all looked up to; he was the only professional in my family.

SW: So, you are sort of self generated?

KD: Yes

SW: And, you went to college at Yale?

KD: I went to Yale.

SW: So, how was that?

KD: Yale was a great place. I entered in 1965 and graduated in 1969; I became a psychology major, because I love behavior. I did research in a serious way first as an undergraduate. I met a professor named Crowder, who was interested in memory, and I took a lot of courses with him on memory that had a very important influence about what I was going to do over the next ten or fifteen years. We published a paper on lisping; how was the information encoded? Would a lisper encode S's incorrectly because they articulated them incorrectly? And, we found out, in fact, that that is what happened. It was terrific fun and I would go to the elementary schools that were around Yale and do a lot of testing of words that kids could lisp.

We found out that those children were probably encoding things through articulation.

SW: Interesting, I had no idea about this. So, other than the psychological project, did you do any scientific bench kind of work?

KD: I didn't start doing bench research until I got to medical school. Medical school, at that time, was in the throes of major curriculum reform and there was a lot of elective time. So, in our first year of medical school I had every afternoon off, the second year aso we had every afternoon off, and in the fourth year we only had six weeks of assigned clerkships and the summers were free. So, from about the middle of the first year of medical school I started an elective in the pharmacology laboratories.

SW: Is this at Sinai in New York?

KD: At Sinai. I spent every summer working and during my entire senior year at Sherwin Wilk's Laboratory at the bench, I put in a tremendous amount of time working on catecholamines and chromatography. Ultimately, had enough skills that I knew what to do around the GCMS, although, I never ran one myself.

SW: At what point did you finally end up with a sense of your career and where you were going?

KD: Sometime, in those summers when I was in the laboratory, as I became immersed in what was then the literature of the indoleamine and catecholamine hypotheses. I got very excited about affective illness; I knew this is what I had to become involved with. I knew that the place I go for residency has to be a place where I could continue along these lines.

SW: And, where was that?

KD: That was at Stanford.

SW: Was that where we met?

KD: That is where we met. I was told by the Chairman of the Department of Psychiatry at Mount Sinai, who was then Marvin Stein that there is really only one place you should go for your residency and that place was at Stanford, in David Hamburg's department. He said that David Hamburg was changing the face of psychiatry; that it was going to be a neuroscience-based psychiatry and that would be the best place for me going. And, he was right. It was a remarkable place with an extraordinary group of people that came together at that time.

SW: So, when you finished your medical school training you had a sense of where you wanted to go. Had you published any papers before residency?

KD: Yes, I had published a couple of papers on the metabolism of norepinephrine and the relationship of CSF - MHPG to affective disease in both bipolar and unipolar illness. So, I probably wrote four or five papers or

abstracts by the time I had entered the residency that were going to be published from the work I had done.

SW: That sounds great. Tell me about your residency if you would.

KD: Well, Stan, as you and I know it was an unusual residency. I think we were in a golden era; we had the government grants so that we were not service committed people. A stipend was not related to the patients that we had to take care of. We really did as much patient care as we needed to do to learn psychiatry and we had enough time to do research. I was assigned, at some point, to the research unit at the Palo Alto VA and was paid for by a grant of Leo Hollister. That left me with enough time that I could write a career development award to be able to continue my work at the VA and stay for a six year period at Stanford just to suck up all that environment.

SW: So, what intellectual trends developed at Stanford for you?

KD: I think it was the conceptualization of neurotransmitter based disease; a lot of people at that time were looking at catecholamines and indolamines. That was the time, of course, that Axelrod won the Nobel Prize for the study of the catecholamine pathway. And, there were a lot of people at Stanford studying endorphins, enkephalins as well as peptides. I wasn't in the laboratory then. I wished I could have been, but I wasn't, and my work with Hollister was more the traditional psychopharmacology. So, I had to figure out ways to use drugs as tools; a measure of the output might be behavior, CSF, or neuroendocrine measures. The neuroendocrine window was just exploding in those years. Then, I thought that memory was something that people had been looking a whole lot about. That led me to spend a lot of time to think about Alzheimer's disease, although I was also very interested in depression and affective disease.

SW: So, you worked on Alzheimer's disease and it turned out to be useful to you. Do you want to talk a little bit about that?

KD: The work on Alzheimer's really started from my knowing something about memory from being an undergraduate at Yale and working with people that studied memory, reading a lot about acetylcholine and learning some about its role. I remember that I was also fascinated by David Janowsky's paper on intravenous physostigmine. It seemed to me that it was very dramatic that they could reverse mania that quickly. So, I wanted to know why that was happening. And, what happened was, that as we were focusing on acetylcholine to study the biochemical effects, some of the manics that we were studying would say things like their "minds felt clearer and sharper than it ever had before". I thought that was an interesting insight and wondered if that would teach us something about

memory. That led me to meet Richard Mohs, who was another one of these terrific young people at Stanford at this time. We developed a relationship and when I told him that I wanted to study memory and I needed good outcome measures, Rich asked, "Do you know anything about the Sternberg Paradigm"? I said, "No." So, he set it all up and we began together to study the effects of physostigmine on normal people. It led to an extraordinary result that I thought came out of science fiction; Stanford students were doing better on the Stanford paradigm, learning more words on physostigmine than when they received placebo in a double-blind study. That led to a publication in *Science*. At the time that paper was being written, there was a publication that in Alzheimer's disease there was an important neurochemical deficit in acetylcholine. So, the last paragraph of my paper in *Science* said that our work has important implications for the therapeutics of Alzheimer's disease. It led to a whole industry devoted to that notion, and a whole bunch of drugs that were ultimately developed around Alzheimer's disease. We continued our work with physostigmine that led to many fruitful efforts. I was awarded for it with one of the first NIH funded Alzheimer's Disease Centers, as well as I was recipient of the Elkes and Efron Awards of the ACNP.

SW: Eventually, if I remember correctly, you ended up participating in the FDA-studies involving the first Alzheimer's compounds.

KD: What happened was that our work was the first proof of the concept that cholinesterase inhibitors could improve symptoms of memory problems in Alzheimer's disease. That was a springboard. And when Will Summers published a small paper in the *New England Journal* that said he had improved with a cholinesterase inhibitor patients with Alzheimer's as dramatically and robustly as L-DOPA improved Parkinson's patients, there was uproar and an outcry from families affected with Alzheimer's demanding to know if this could be true. NIH contacted the directors of the Alzheimer's research centers and said, you guys need to figure out if this is true. Since my colleagues and I already had written a grant not to use tacrine but to use an other cholinesterase inhibitor, oral physostigmine, to prove that cholinesterase inhibitors could be a practical treatment for Alzheimer's disease, we were the obvious center to coordinate a multi-center trial. That is exactly what we did, and in that trial it was again shown, but now on hundreds of patients, that a cholinesterase inhibitor could really work. And, you know, that led to the approvals down the road of donepezil, rivastigmine and galantamine.

SW: That's really nice. I, personally, would say that I saw your interview; I think it was on NBC at the time. I really enjoyed it. So, what did you do after you moved from Stanford?

KD: Well, I have always been fascinated with schizophrenia. I have always taught people who worked with me that we needed two trains going. So, while there was an Alzheimer's group going, we also had a schizophrenia group going. Early on, that was still around dopamine and plasma HVA, that we collected brains, because I believed that, without studying brain tissue you don't really know what is going on in the brain. So, I really wanted to collect brains from a group of schizophrenic patients. I was fortunate that in 1987, I met some people who ran the Pilgrim Psychiatric Center. Pilgrim's was a very strange place; it was like the land that time forgot. It was once a place with 17,000 patients, located on hundreds and hundreds of acres. It was also associated with two very large psychiatric hospitals that were in the eastern part of Long Island. Together, there was over 35,000 psychiatric patients in that region in the mid-1950s, but by 1987 it had narrowed down to two 2,000 thousand and of those 1,000 were over the age of sixty five. And, that said to me right away, my goodness, here is a group of people that will die in the hospital and we could have the greatest collection of brains that anyone had together with the patients medical records. Little did I know in 1987, that about thirteen years later genetic research will have the capacity to study molecular changes in the brain in a way that were un-thought off at the time. So, as the Alzheimer's research took its' on course and I had to do more and more administration, I shifted my focus on schizophrenia.

SW: I'll add a little comment here. Your time frame for collecting brains is sort of matching the onset of the completion of the genome project. Acquisition of samples is an extremely critical issue in the kind of research you are doing.

KD: It takes a long time! And, we have the records of these patients. Further, we interview each of our patients every year with a four to six hour interviews. I think people don't fully appreciate the necessity to have detailed characterization of the phenotype in genetic research. And, since we find now so many genes with low penetrance and low overall genetic contribution to the disease we will probably need to dissect further phenotypes, to a narrower and narrower degree from our data base.

SW: To jump ahead a bit, could you say something about your methodology and findings?

KD: Well, we took a very empirical approach to the "micro-array" studies. When we did around the first six thousand genes, we found that there were a few hundred that were either over or under expressed. To make sense of that is very difficult. But, as you know, they were increasingly sophisticated statistical programs and by using those we grouped together biologically related genes. And, by doing that the only group

of biologically related genes we found under expressed as a group were those that were related to oligodendrocyte function and myelination. Just before I became Dean at Mount Sinai, I sat in my basement for about three weeks. It was an amazing period of insight and productivity during which I wrote my first Conte Center application, based on those first microarray data. All our findings pointed to the role of myelin in schizophrenia. The pertinent question was whether there was a dysmyelination syndrome in schizophrenia. That led to our first Conte Center grant application.

SW: So, you have indicated that you have shifted towards more administrative activities. I want to ask a general question about those efforts, such as the administrative tasks you have taken on. And, perhaps, also whether some people might have influenced you to move in that direction?

KD: One of the things I learned at Stanford was that if you didn't control the clinical flow, you couldn't do clinical research. So, when I left Stanford and I was looking for various places I could go, although, I wasn't looking for an administrative job, I was always looking for enough authority to make sure there would be the right culture to facilitate science, academic medicine and research. That conviction led me to become the Chief of Psychiatry at the Bronx VA and to bring with me someone to run part time the day-to-day service while also part of the research team. That person was Tom Horvath. So, together, we were handed, at a very young age, a fairly large psychiatry service to run at the Bronx VA. I learned that it was the right decision because to run an inpatient research unit, and to do outpatient research, you just have to have the authority. The Bronx VA was part of Mount Sinai, so, when our chairmanship changed at Mount Sinai, I turned around to our group and asked what should we do? I didn't feel an eagerness to become Chairman, but I was very worried that they could get another Chairman who would not be at all as sensitive and facilitating of our research as our previous Chairman. Our group all agreed that I should become Chairman as long as I could find someone like Tom Horvath to help with the day-to-day management of the inpatient unit. I did that and we continued to grow the research base; it was always a research and neuroscience driven department. I didn't know that I would enjoy the day-to-day management of running the department, but what I knew was that I enjoyed the science and working with young people and running the laboratory. Around 2001, I had already been Chairman for fourteen or fifteen years and I, then, asked myself, was this, what I wanted to do for the rest of my career or was there something else more that I wanted to do? With not great certainty, I decided it was okay to put myself in the running to be the Dean at Mount Sinai. I was offered that job toward the end of 2002 and became the Dean in the beginning of 2003.

But, two months later, our Board fired the CEO, and asked me if I would do both jobs, being the CEO, and the Dean, which is a lot of work, more than I had ever thought. So, I did that for a few years. Ultimately, found someone else to be the Dean, Now I am just the CEO of the Medical Center. And what I found is the being the CEO of the Medical Center is far more fun than being the Chairman of Psychiatry, because at Mt. Sinai the Medical Center is the over-arching institute for the hospital and the medical school with both reporting to me. This made possible to do really good things. It's an enormously efficacious position. I have no university President to report to and I don't fight with the Dean, because the Dean reports to me, and I hire good people. So, this has become a part of my career I had never thought I would do, but has been enormously rewarding. What I miss is that I can't keep doing the Conte Center research as much as I would want to do, so in the second renewal of the Center I couldn't be the PI any longer.

SW: So, who is the PI?

KD: Joe Buxbaum is the PI; I am the Co-PI. I spend a few hours a week watching what happens, at the Center.

SW: So, as the CEO, how do you see yourself in terms of the general research environment at Mount Sinai?

KD: Mount Sinai is a special place. We are like a biomedical college. We don't do anything else. We take care of patients, we do science and we teach people how to become doctors or medical professionals. That's an environment in which you can have a tremendous impact. So, when we make decisions about where we will invest, and we are very fortunate because we have very generous donors that we have had for a very long time, it is now possible for us to do things that would be undreamt of before, like establishing a brain institute, or a stem cell institute, or an experimental therapeutic institute, and spending a lot of money on diseases that I didn't know very much about, as for example cancer. Additionally we have created an environment that really makes it possible to translate ideas from the clinic to the lab, so, that we can get better diagnostics and therapeutics for making a difference in people's lives. Done right, I think my position really does have the opportunity to make a big difference in medicine.

SW: That's fascinating. How much of Mount Sinai's - investment, if you will, can be found in fundamental science, more or less unrestricted in content vs. translational research?

KD: Well, that is a very difficult and important question. We are not a university, and since we are a hospital that gave birth to a medical school, and our philanthropy often derives from grateful patients or trustees because of patient care, it is less easy for us to fund fundamental research than

for, say, Cold Spring Harbor Laboratories, forty miles east of us. It's a lot more justifiable in the eyes of our trustees for us to say that the basic research we do is around diseases, even, if it is multi levels removed from disease. So, we can study drosophila and we are happy to study drosophila, because people understand the implications of that for human disease. We can study chromatin because of the implications and what that means for human disease. But, we leave to the larger universities, some of the more basic questions and, with that said, we still have a portfolio of research that is a quarter of a billion dollars just for funding science. That is not funding the infrastructure that goes to salaries and to supplies for scientists.

SW: So, is this money from NIH or from private sources?

KD: It's about 230 million NIH funding and the rest from philanthropy and other foundations.

SW: Sounds like a reasonable mix. So, back to your sciences: what is your most important contribution to the field? What am I going to remember Ken Davis for?

KD: It's the proof that cholinesterase inhibitors are effective in Alzheimer's disease. You know, we developed the scales people use, for assessing changes, the methodology for the studies, conducted the clinical trials with these drugs, and presented the proof. And, as much as we have tried to find other drugs, we have largely failed. The question, whether cholinesterase inhibitors have some effect on the course of the disease, I think we will never resolve. It's disappointing that no other drugs have been developed. Regarding schizophrenia, my greatest contribution is the insight about the involvement oligodendrocytes and myelin; and that this disease, which undoubtedly affects multiple brain regions and multiple systems, is possibly a disconnection syndrome.

SW: Time will tell.

KD: Time will tell.

SW: So, do you have any comments on your publications? Have you ever been a journal editor?

KD: Well I have been; I am an editor now, one of the editors, of the *Archives of General Psychiatry* and I have been an editor of the *American Journal of Psychiatry* and *Biological Psychiatry*, but I have never been the chief editor of any journal. By and large, as a field, I think we do a great job of disseminating information. We have seen in our lifetime the advent of the information on the internet and clearly it's changing the way we publish and the way that information is disseminated. Perhaps, there will be a lot less consideration to the journal you put your paper in, as opposed to it being just widely out there so that everybody can access it.

SW: Do you advocate publication of supplemental large data sets of studies?

KD: I think it's important to publish large data sets. I think people should be able to mine them for the right answers. The worry that this could be abused for favoring one product over other products should not stop the dissemination of this information. I think it would be useful if users stipulate, a priori, what they want to mine, so that their hypotheses were also established in the public domain. Then we wouldn't have people just dredging away until they get an outcome that they want, or using computers and statistics as a tool or as a weapon to get the answer that they would like instead of honest findings. It would be an even playing field and unbiased approach.

SW: Have you put the data of your micro-array studies in the public domain?

KD: Yes.

SW: What honours have you received over the course of your career?

KD: Well, I have been fortunate to receive a lot of honors. I have received, as I mentioned it before, the Efron and Elkes Awards from the American College, and receiving this year, the Hoch Award for service to the college. I have received the Kempf Award from APA, and I guess a bunch of other awards from others.

SW: Are you involved in any other major professional organization beside the ACNP?

KD: Well, in science, this is my most important organization and it has always been. Over the years I have become less involved in the Society of Biological Psychiatry. I have gotten involved in things like The New York Academy of Medicine, and the Greater New York Hospital Association, that brings together all the New York City medical centers. I am on the board of both, and also a trustee of the Academy. I was the Chairman of the Board of the Greater New York Hospital Association and I am also involved in things like the University Health Consortium and the Society of Medical Administrators.

SW: You also have kids and you are married. What has the impact of your many activities on your family?

KD: I have been very, very lucky, because I married a great woman, Bonnie Davis. We knew each other since she was ten years old and we have often said when we first met in seventh grade no one would have dreamt that we would get married, that she would have become so enormously successful with galantamine, and I would become the CEO of the Mount Sinai Medical Center. We have always worked together. She wanted to be an endocrinologist, with a perspective on the neuroendocrine function, and what endocrinology can teach you about behavior. So, we fit together in research and we fit together personally. Our children grew up

in this environment with two scientists who were very, very involved in their work. But, Bonnie, in 1987, said our children need me and I have got to stop working. She said, I am going to work from home, will develop my drugs and patents from home, and if it doesn't succeed, then, it doesn't succeed, but the children are more important. I always took the position that our children came first, their soccer teams, and everything else they did and their golf so I would just get up and leave work to be with them. So, the family has been very tight.

SW: How did this whole thing work out, your professional life and your family life? Are you happy or are you unhappy?

KD: I am a very fortunate person. You know, I just turned sixty and it has been a remarkable run. It is hard to believe that I am sixty, but as I look back on it, it couldn't have been better. As long as my kids and wife stay happy and healthy, things will continue to be great.

SW: You are in a very powerful position in terms of perspective to think toward the future. You have seen a lot of progress in the field, so where are we going in the next five to ten years.

KD: I worry a great deal about the future of our field and about the future of medicine. Let me give you some examples. No matter what we think, a lot of our work is dependent for its infrastructure support on the health of our large medical centers. Medical schools are money losing propositions. On a good day, they break even, but on a bad day, they lose three to five percent of their top line. They are supported, by and large, by states, by incredible endowments or by hospitals that spin off the dollars to support them. Those hospitals often find, themselves, because they are old rich hospitals in urban centers, that they serve large impoverished populations. So, at a place like Mount Sinai or Presbyterian Hospitals in New York it is not unusual to have sixty five percent or sixty percent of the population being served, either Medicare or Medicaid patients. Medicare and Medicaid dollars go up one to two percent in an average year. The cost of doing business with those hospitals goes up five to eight percent, on average, a year. We have an unsustainable business model. And, there is no sensitivity on a national level to the consequences of slowly bankrupting our great academic medical centers. You add to that two other factors: the budget from NIH is shrinking in real dollar value and the cost of health care is increasing in America as America ages. We can't afford all the care we are going to need and we have to find a way to do it. The priority for research and science seems to become lower and lower. So, how is this going to be sustained? How can we make sure that we have real breakthrough drugs?

SW: Magic bullets...

KD: I think we have to speak much more loudly and effectively for what are the long term benefits of scientific breakthroughs of medicine. The problem is we have had too many wars on cancer and decades of the brain. And, at the end of those wars and decades we haven't produced innovative compounds. I think we were forced to oversell that would come out of those wars and decades. The public has misperceived what we can and can't deliver and whether we have the ability to invest for the next generation.

SW: So, this is near the end of this interview, and I have one global question: What didn't you tell me?

KD: I didn't tell you about some of the people of whom I am indebted to.

SW: Go for it.

KD: From Leo Hollister, I learned how to be ethical, honest and of uncompromised integrity. For Leo the data were what the data were; he was just a terrifically good and honest man. And, for David Hamburg, who has been an extraordinary figure in and out of my life, as of yours, comes the notion that psychiatrists can solve big problems. We can also deal with questions like why is there genocide in the world, and how do we make this a better place for all of us to live. Psychiatrists have the ability to solve those problems and I think he has been a role model for all of us. And, there is one other thing. We have been very fortunate, you and I, and a few of us, to have developed friendships and colleges like this one. Even though we meet each other maybe once or twice or three times a year at various places, the friendships are enduring for a lifetime. Some of the most valuable relationships and friendships I have are with the people I have known in groups like this and, you know, I will take those to the grave.

SW: Very good, thank you, Ken.

KD: Thank you.

MICHAEL H. EBERT

**Interviewed by Benjamin S. Bunney
Scottsdale, Arizona, December 8, 2008**

SB: My name is Steve Bunney, and I am interviewing Michael H Ebert.* This is the 47th Annual Meeting of the American College of Neuropsychopharmacology (ACNP) in Scottsdale, Arizona, and the date is December 8th, 2008. So, Mike, I thought we might start at the very beginning, and that is where you were born and, particularly when you were growing up, what influence your mother or father or siblings might have had on the direction that your career took.

ME: Very good, so this is a psychiatric interview! I was born in Boston on March 23, 1941, around the time that the United States entered the Second World War. My father was a research fellow with Gene Stead at the Peter Bent Brigham Hospital at that time.

SB: He was trained in internal medicine?

ME: Yes, my father and my uncle both attended medical school at the University of Chicago, and both were house officers at the Boston City Hospital and its distinguished Thorndike Laboratory. After training in internal medicine, my father, at the time of my birth, was Eugene Stead's first research fellow. Eugene Stead went on to become the Chair of Medicine at Duke for decades, trained numerous leaders in internal medicine, and helped build Duke University School of Medicine. My mother was a social worker and we lived in Cambridge, but my father quite promptly went overseas with a Harvard Medical School unit that stayed together in the European theater for almost four years. He went over to Normandy three days after D-Day to establish the first US Army field hospital after the invasion. My father was awarded a bronze star for his research on hemorrhagic shock, research which was conducted before and after the Normandy invasion.

SB: Wow!

ME: That was the beginning of my father's influence on me. My parents were divorced, so I moved around the country quite a bit, living with my mother, and visiting and sometimes living with my father and stepmother.

SB: So, your father was deeply involved in research. And, do you remember that? Do you remember that as something you heard a lot about?

ME: Yes, my memories of his research activities go back to my 10th year of age or so. My father had a very distinguished career in the Veterans Administration Healthcare System (VAHS) over two separate periods in his life. He was chair of two medical school departments of internal

* Michael H. Ebert was born in Boston, Massachusetts in 1941.

medicine, but every year that he was not a chair, he occupied a position in the VAHS. He started out as the Chief of Medicine at the Minneapolis VA immediately following the end of the war. Academic medicine and the VA were both on small scale in the late 1940s, and the VA academic affiliations had just begun. My father assembled a brilliant group of people with him, including Carlton Chapman, who eventually became the Dean of Dartmouth Medical School. My first memories of scientific activities with my father were when we were living on the grounds of the Minneapolis VA. I was beginning my electronic hobbies, building short wave radios. After supper, we would go back to the electronic laboratory at the VA, and build circuits together. Around the same age, I remember my grandfather teaching me physics and fishing (!) on our summer vacations in the north woods of Minnesota.

SB: Okay.

ME: And then my father went on to be the Chief of Medicine at the new Lakeshore VA Hospital in Chicago, when it was called the Research VA Hospital and a Professor of Medicine at Northwestern University School of Medicine. From there he went to the University of Arkansas to be the Chair of Medicine at a small and young medical school, and recruited a group of talented physician scientists from all over the country. After 12 years or so, he went back to the University of Minnesota as Chair of Medicine where he ran a large department of medicine. When, he retired from the Minnesota Chair, he went back to Arkansas as a Distinguished VA Research Professor.

SB: Well, it seems to me as we go along we are going to see some themes here that we will pick up as we travel through your career. So, just in summary for just that part of it, you would say then that your dad did have an influence on you in terms of any future career choices?

ME: Yes, and at some point I will tell you about my other mentors.

SB: We will get there in a minute.

ME: But my father and uncle were probably my most powerful scientific mentors.

SB: Right. So, you have traveled around the country a fair amount, and we will skip high school and go on to college. Where did you go to college?

ME: Williams College in Williamstown, Massachusetts.

SB: What was your major?

ME: English Literature. On the psychological theme that you have introduced, I was having a conflict in college about what career to pursue because I come from a family of academic physicians, including my grandfather, as well as my father, and my uncle, and I was somewhat apprehensive

about going into medicine, particularly internal medicine. I was majoring in physics. At the last minute, in the summer between my junior and senior years of college, I found a summer job at the Massachusetts Mental Health Center with Leston Havens, a distinguished Harvard Medical School psychiatrist. That summer I figured out that perhaps, if I went into psychiatry, I could pursue a different path in medicine from others in the family. That was one of those intuitive decisions that was quick but worked out well. Still waters run deep!

SB: What did you do during that summer?

ME: I was a participant observer in a sociological study on psychiatric patients and their experiences in the hospital. I wrote up short essays about them on the basis of our interactions on a day to day basis. The only slight problem in deciding then to go to medical school was that I didn't have any pre-med courses, but I went back to Williams and finished up in English Literature because I had about the same number of courses in that field as I had in physics, and I also took freshman biology and chemistry. I applied to two schools of medicine, and got into Western Reserve School of Medicine in Cleveland, but did not get into Yale! I took organic chemistry at Harvard Summer School and then squeaked right into Western Reserve, which, at that time, was a very interesting and liberal medical school. During that decade Western Reserve probably produced more academic psychiatrists than any other medical school in the country.

SB: So, you didn't lose a year; you just crammed the entire pre-med courses into the remaining time that you had, plus one summer.

ME: Yes.

SB: Wow!

ME: And, I had a little bit of a rocky start since I hadn't taken too much chemistry. Paradoxically, as the scientific activities in my career developed later, I became a neurochemist and clinical pharmacologist.

SB: Right.

ME: And, I did research, neurophysiologic research, in medical school with Chris Gillin, who was one of my best friends.

SB: With Chris Gillin?

ME: Yes. After I finished Western Reserve School of Medicine, I stayed at the University Hospitals of Cleveland for my internship, and then I went off to the Massachusetts Mental Health Center, which I had developed affection for from the college summer when I'd worked there. At the time, MMHC was one of the best Harvard Medical School psychiatric residencies.

SB: And, so you did your residency there? Those were days when the residency and internship were separate?

ME: Yes. I did my internship at University Hospitals of Cleveland. I did a straight medical internship and then started a psychiatric residency at Harvard Medical School.

SB: Did they give you stress interviews in those days, to get into the program?

ME: No, but I had an entertaining interview with Jack Ewalt about sports cars! They did stress interviews for the medical school.

SB: They did for me when I was interviewing!

ME: They did for the medical school. My uncle had been the Chair of Medicine at Western Reserve and moved to Harvard Medical School in 1964. He was recruited to be the Chief of Medicine at the Mass General and then a year later became the Dean of Harvard Medical School. When I arrived in Boston, he had recently become the Dean of Harvard Medical School.

SB: What was his name?

ME: Robert Ebert.

SB: And, if I look at your CV you also spent time at the Mass General?

ME: Yes.

SB: And, was that part of your training, or...

ME: Well, necessity is the mother of invention.

SB: Okay.

ME: I was trying to combine thorough clinical training in psychiatry with initial training for a research career. However, in my application for deferment for military service, as you recall there was a doctor draft during those years, I didn't get a full Berry Plan in the United States Army, and the Vietnam War was well underway. So, at the Mass Mental Health Center I was going from year-to-year, with some risk of going to Vietnam. At the end of each year there was a chance of going to Vietnam, because there it was a lottery process at that time. Towards the end of my residency, I realized that some people in the Harvard program were not going over to Vietnam at the last minute for unusual reasons. So first of all I was successful in extending my residency. I started out working with Dick Shader, who was my first scientific mentor in psychiatry. Dick and Carl Salzman taught me a great deal about psychopharmacology and execution of clinical trials. Seymour Kety had just come to the Mass General, and I arranged to have what was a PGY-V year. In my PGY-IV and -V years, I was awarded the DuPont-Warren Fellowship, which was a Harvard travel fellowship, and used it to travel to the Mass General!

SB: And your draft board allowed you this extension for a year?

ME: They did. And so I became one of the first five fellows in Seymour Kety's laboratory, and Ross Baldessarini was my research mentor. So now we are collecting mentors.

SB: Yes.

ME: So, then I realized that others were not going overseas, for various reasons, and I got myself into the office of the Army officer who was running the Berry Plan, in the James Forrestal building in Washington DC. I explained to him that I wanted to be a psychiatric researcher, and wanted to ask if I could get a conditional release to obtain a commission in another military service. I thought at first that I would try to go to the Walter Reed Institute of Research, but later on I decided to go into the United States Public Health Service in order to go to the NIH. The man running the Berry Plan was sitting there with a blackboard with names of doctors on it. After some discussion and a little carrying on, I ended up getting a conditional release, which was unusual in 1970.

SB: Wow!

ME: Most physicians didn't know what a conditional release was. I had six months to find a commission. I went all over the federal government, and Seymour Kety was a great help to me. Finally, in the fifth month, I got an interview with Irv Kopin, and he gave me a fellowship position as a Staff Fellow in the Laboratory of Clinical Science.

SB: Wow! That is quite a story, actually!

ME: So, that is how I got to the NIH.

SB: Okay. So, you started in his lab. So what date are we now on?

ME: That was 1971.

SB: Okay.

ME: And, I had already been getting some psychopharmacology training with Dick Shader and neuropharmacology training with Ross Baldessarini.

SB: With Rocky Ross, yeah.

ME: As well as Seymour Kety. That was clearly the beginning of my formative years in psychopharmacology. It was a wonderful environment. I was learning all the assays for catecholamines that were current at that time. We were running alumina columns and doing fluorometric assays to measure catecholamines, indoleamines, and their metabolites. Then I arrived at the NIH. Many physician scientists were there whom you know, including your brother, Biff, who was running the NIMH research wards as Chief of the Adult Psychiatry Branch, Fred Goodwin, Dennis Murphy, and Tom Chase. Irv Kopin wanted one or two people in the Laboratory of Clinical Science to be working somewhat more on clinical pharmacology as a discipline in its own right. And that was really how I developed an identity as a central nervous system clinical pharmacologist, which I have kept somewhat separate from my identity as a psychiatrist. Irv actually gave me the idea; he talked to me for about two months, and had a style of offering advice that was brief and pungent. Finally, one morning he said, "Mike, you need to be a clinical pharmacologist". I needed some

guidance at that point, and I said, “That’s fine, I’ll do it!” And so he gave me a little lab and also arranged for me to work with Edna Gordon as a mentor. Edna Gordon ran the laboratory that supported assay development in the Laboratory of Clinical Science. Over a period of three or four years he began buying me some equipment. He bought me a gas chromatograph, and I had to unpack it and make it work. A little later on he bought a mass spectrometer, and he sent me in there and taught me how to run it. So, I was working in parallel with the clinical scientists in the Adult Psychiatry Branch, doing clinical and basic neurochemistry. We started to work on some methodological experiments on how to measure the metabolism of neurotransmitters in vivo, to be able to pursue various hypotheses regarding the neurochemical etiology of psychiatric and neurological disorders.

SB: Irv was pioneering some of those studies, at that point, if I remember correctly.

ME: Yes, he was. Over those years, I conducted, with Irv and other collaborators, a number of studies in which an attempt was made to measure central nervous system metabolism of neurotransmitters by labeling techniques. The first study of this sort was conducted with Irv during my fellowship in clinical pharmacology. The study was conducted in human subjects and depended on the fact that radiolabeled dopamine infused intravenously does not enter the central nervous system, and that the labeled dopamine can only be converted to labeled norepinephrine in noradrenergic neurons that contain dopamine- β -hydroxylase. The study led to initial estimates of the contribution of central nervous system norepinephrine metabolism to urinary excretion of the catecholamine metabolites, MHPG and VMA. We also worked on a variety of stable isotope labeling strategies with gas chromatography-mass spectrometry analysis of catecholamine metabolites, to determine in vivo turnover rates of brain catecholamines in rhesus monkeys and human subjects. We were successful in this effort in rhesus monkeys, using serial samples of lateral ventricle cerebrospinal fluid, but were not successful in developing a clinical research technique for humans because of the need for multiple data points over hours to calculate rate constants. In a later study, we infused deuterium-labeled MHPG into human subjects to determine the relative contribution of central nervous system and peripheral sources of norepinephrine to urinary excretion of MHPG. At the time of this study, there was a good deal of clinical research on depression, utilizing MHPG excretion in the urine as an index of brain norepinephrine metabolism. We demonstrated that about one fifth of urinary MHPG is derived from the brain and that free MHPG in the circulation can be converted to VMA.

- SB: Who else was in the Laboratory of Clinical Science at that point in time?
- ME: Well, I was up on the third floor next to Edna Gordon's lab. Sandy Markey was next door, as was David Jacobowitz. Julie Axelrod was down on the second floor; Joe Coyle and Steve Paul were in his laboratory. The fellows, or post-docs, consisted of PhD pharmacologists and neuroscientists, as well as a collection of physicians trained in internal medicine, neurology, psychiatry, anesthesiology; all learning neuropharmacology.
- SB: I am looking for other people in the ACNP.
- ME: Many current members of the ACNP were on the various NIMH wards and laboratories in the NIH Clinical Center during that time: Bob Post, Dave Jimerson, Jim Ballenger, Bob Belmaker, Wade Berrettini, Monte Buchsbaum, Burr Eichelman, Elliot Gershon, Phil Gold, Bob Golden, Tom Insel, David Jimerson, Ned Kalin, Ray Lake, Jim Leckman, Al Lewy, Steve Marder, John Nurnberger, Candace Pert, David Pickar, Bill Potter, Gene Redmond, Peter Roy-Byrne, David Rubinow, Larry Siever, Tom Uhde, Daniel van Kammen, Tom Wehr, to mention some of them. .
- SB: Quite a group! Just to understand, when you got that job, it was in lieu of service? How long of a commitment did Irv make with you at the start?
- ME: It was a two to three year neuropharmacology fellowship that included military service in the United States Public Health Service.
- SB: Right.
- ME: Paradoxically, I had strong reservations about the Vietnam War, as did many of my colleagues. You tell me if I am going on too long here?
- SB: No, it's fine!
- ME: Do you remember the Physicians for Social Responsibility?
- SB: Of course!
- ME: And, Bernard Lown, a distinguished cardiologist at the Peter Bent Brigham Hospital, was the leader of that organization at the time.
- SB: Right.
- ME: So, back in Boston during my residency, Physicians for Social Responsibility was a small group, and I was a member. It was just beginning as a political group, and it was very exciting. We met in Dr Lown's living room once a month. Then, one evening, Bernie Lown said, "This is what we have to do. We have to get more aggressive and we have to make a statement, and we need some young people to go to jail". And, then he said, "Mike, you would be a candidate!" So, I called up my father, the academic doctor, and in an optimistic and enthusiastic way explained that to him. That was an extremely unpleasant telephone conversation!
- SB: I am sure! I am sure! I guess he suggested that you also talk to a lawyer.
- ME: But anyway, the reason that I told you the story is that, by happenstance, I got into a military commitment, and when I finally left the NIH after 13

years, I was 13 years into a military retirement. A lot of physicians did not leave the NIH with that amount of time in a USPHS retirement.

SB: No!

ME: But at the end of my time at the NIH, I was looking at psychiatry chairmanships, and it seemed to be the right time to leave and take a chairmanship. That led me, out of an interest in completing my military retirement, to take a deep breath, and join the Active Reserves of the Navy. I am now a retired Navy Captain.

SB: A Captain, right. So, let us go back to your time with Irv and also whatever research that you think is important and would be very interesting to hear about. But also, then, you know you got promoted and you became...

ME: So then let us do the second part of this first. The other part of that story was at the time, as you know, the NIMH was one of the most exciting places in the country for psychiatric research training, and there weren't too many others, with Yale being one of the few others. But, there were not too many university environments that provided opportunities for that kind of growth and development in neuroscience and neuropharmacology. Therefore, it was a fortuitous opportunity for me to be invited to remain on the permanent scientific staff of the NIMH at that time. The Laboratory of Clinical Science in the NIMH Intramural Research Program (IRP) was assigned five research wards in the Clinical Center. One ward was connected with the Section on Experimental Therapeutics, and was run by Tom Chase. Biff Bunney, your brother, was in charge of the other four wards along with Fred Goodwin and Dennis Murphy. Then Tom Chase became the Scientific Director of the NINCDS IRP.

SB: Yes, right.

ME: So, that career move created an opportunity for me to stay at the NIH, although the process of becoming a member of the permanent NIH staff developed through two acting positions.

SB: So, that opened that position.

ME: Yes. Irv Kopin was looking for an investigator who would focus the clinical research unit on clinical pharmacology, and be a training site for physician scientists from a variety of clinical specialties, including psychiatry, neurology, and internal medicine. So I got that job on an acting basis for two years, and took over Tom Chase's ward, with the understanding that I would not conduct research in the areas of depression and schizophrenia. That opportunity cemented my clinical pharmacology agenda. So, I worked on neuropsychiatric syndromes, psychosomatic syndromes, and clinical methodologies to study neurotransmitter function and metabolism. Edna Gordon's clinical neurochemistry laboratory and Sandy Markey's mass spectrometry laboratory were key elements in

this effort. I had a small laboratory that was physically located between the Gordon and the Markey laboratories. I developed a clinical research program, and the fellows that I had were psychiatrists, neurologists, and internists. They were not all psychiatrists.

SB: Interesting. Didn't you do some nice challenge experiments with amphetamines? Weren't you able to manipulate the noradrenergic system and demonstrate that you could study its function in vivo?

ME: That was a different series of experiments with Ray Lake and Michael Ziegler, who became close colleagues of mine. Ray Lake, an ACNP member, eventually became the Chair of Psychiatry at the University of Kansas, and Mike Ziegler has been a Professor of Internal Medicine and Pharmacology at UC San Diego for a long time. We began to work together on methods to measure the very low levels of catecholamine neurotransmitters found in the cerebrospinal fluid, using radioenzymatic assays. At the time it was thought that these molecules were both too unstable and also so subject to extraneuronal metabolism that they would not be present in CSF. Several years before we began these studies, I had set up a primate laboratory to do in vivo studies of brain metabolism using serially collected samples of lateral ventricle, cisternal, and lumbar CSF. I developed a technique for cannulating the lateral ventricle of the chaired rhesus monkey and collecting continuous samples of CSF for days or weeks at a time. We began to use lateral ventricle levels of norepinephrine to draw conclusions about brain metabolism of norepinephrine. We found that we could measure levels of norepinephrine that were stable and reproducible in the picogram range using radioenzymatic assays and later high pressure liquid chromatography assays using electrochemical detection. We then proceeded to conduct a series of physiological and pharmacological experiments to determine the utility of the technique. We reported the ability to measure norepinephrine reliably in lateral ventricle cerebrospinal fluid, and the presence of a diurnal rhythm of norepinephrine levels in primates and in lumbar cerebrospinal fluid in humans, that reflected the known diurnal rhythm of norepinephrine synthesis in the brain. We also demonstrated that norepinephrine in the circulation did not cross the blood-brain barrier, whereas MHPG did.

SB: Right.

ME: We went on to demonstrate that the known pharmacological effect of amphetamine on releasing norepinephrine from central nervous system noradrenergic neurons could be demonstrated in serial samples of norepinephrine measured in lateral ventricle cerebrospinal fluid. We also studied the differential effect of release on the two stereoisomers of amphetamine. We showed that you could do pharmacodynamic

experiments with this model. An amphetamine challenge, administered intravenously, produced a beautiful curve of release in the lateral ventricle CSF. We subsequently did a series of studies in which we measured norepinephrine and dopamine- β -hydroxylase in serial samples of lateral ventricle CSF. We showed that you could demonstrate in vivo the pharmacodynamics of a tricyclic antidepressant. In this study we had the idea that we might be able to measure the release and reuptake of norepinephrine from central nervous system neurons by measuring norepinephrine and dopamine- β -hydroxylase (DBH) protein concentration simultaneously in serial samples of lateral ventricle CSF. Norepinephrine and DBH are released in a quantal manner from the presynaptic neuron. Norepinephrine in the synaptic cleft is subject to changes in the reuptake mechanism of the presynaptic neuron. DBH, a protein, would not be affected by changes in reuptake after it is released. The study documented the known pharmacodynamics of a tricyclic antidepressant over the first several weeks of treatment, with the initial potent effect on reuptake, indicated by norepinephrine levels, and the later adaptive change in the decreased firing rate of the presynaptic neuron, indicated by changes in DBH. It was an elegant study!

SB: It was! I remember reading about this and thinking, boy, this is a step forward. And, actually, I think that, out of those studies, came a whole explosion of experiments all over the world.

ME: I think so. We went on to apply these techniques to in vivo neurochemical studies of primate models of psychiatric and neurological diseases, and to apply them in clinical studies of a variety of diseases from orthostatic hypotension and essential hypertension to major depression, anorexia nervosa, and bulimia nervosa. Subsequently, we were able to measure very small amounts of dopamine, dopamine sulfate, and serotonin in CSF.

SB: What other methodological experiments did you pursue with CSF neurochemistry?

ME: In the middle of my years at the NIH, I developed collaboration with a basic science colleague, Carl Merrill. We worked together to secure an intramural grant from NIAAA, as part of their effort to start a clinical research program on the NIH campus. We then recruited a research fellow, David Goldman, who is now a senior scientist in the NIAAA Intramural Research Program. Dr. Merrill had been working on two-dimensional gel electrophoresis for several years. We decided to adopt the technique to look at very small amounts of brain proteins. We also wished to see if brain-specific proteins could be identified in cerebrospinal fluid, and if alterations in the amount of these proteins could be studied in disease states. To accomplish these goals, the methodology for staining the proteins had

to be adapted to be much more sensitive than staining procedures that were currently in use. We published the silver stain for polypeptides that we developed for the purposes described above. It was a photochemically-derived silver stain that could detect as little as 0.01 nanogram of protein per square millimeter. We then reported our detailed analysis of cerebrospinal fluid proteins. We resolved over 300 polypeptides from 60 microliters of cerebrospinal fluid. By comparing electrophoresis of cerebrospinal fluid and plasma proteins, we drew inferences about brain-specific proteins. We went on to apply this technique to etiological studies of a variety of diseases, including Lesch-Nyhan syndrome.

SB: That is very interesting!

ME: Yes!

SB: So, some of that work was done with Irv Kopin?

ME: Yes.

SB: And, then you began to direct your own research program?

ME: Yes. I was Chief of the Unit on Clinical Pharmacology briefly, and then Chief of the Section on Experimental Therapeutics which was an independent group and clinical research operation within the Laboratory of Clinical Science.

SB: Section Chief.

ME: And, that is when we began to study Huntington disease, Parkinson's disease, and a variety of psychosomatic syndromes. We also continued to work on methodologies to study neurotransmitter function in vivo. I initiated a program of research on the neurobiology and psychopathology of anorexia nervosa and bulimia.

SB: Yes.

ME: I thought that anorexia nervosa was fascinating because it was an acquired illness that was almost impossible to treat.

SB: Right.

ME: I had four major collaborators in these studies over the years: Walter Kaye, Harry Gwirtsman, Philip Gold, and David Jimerson. Drs. Kaye and Gwirtsman were originally research fellows in my clinical research program at the NIH. We set out to elucidate what we suspected was a secondary neurobiological syndrome in the chronic phases of anorexia nervosa and bulimia nervosa. As in endogenous depression, we felt that this syndrome might define many of the stereotyped symptom patterns that are observed, and that understanding the physiology of such syndromes might give clues to new treatment modalities. As it has turned out, the most definite and reproducible neurobiological findings that we reported were changes in brain metabolism of serotonin and norepinephrine, several endogenous opioids, neuropeptide Y, neuropeptide YY, and central

vasopressin secretion. We reported the subtle changes in brain serotonin metabolism that were linked to bulimic behavior before it became known that fluoxetine, a serotonin reuptake inhibitor antidepressant, was efficacious in stopping bingeing and purging behaviors. We demonstrated abnormalities in central nervous system norepinephrine metabolism in anorexia nervosa that are apparent even after long-term weight recovery. Over the years, we demonstrated several types of abnormalities in brain serotonin metabolism in anorexia nervosa and bulimia nervosa, depending on the phase and type of illness. The metabolic abnormalities were not reversed by short-term weight recovery. Anorexic patients who had active bulimic symptoms demonstrated significantly lower indices of brain serotonin turnover than those patients without bulimic symptoms.

SB: Very interesting. It provides a neurobiological background for the therapeutic action of fluoxetine in these illnesses. Now tell me about your administrative activities later in your NIH career.

ME: As you know from our relationship, I have always had an interest in medical education and administration. At one point I was elected as the Chair of the Medical Board of the NIH Clinical Center. In 1980 Robert Cohen retired as Clinical Director of the NIMH Intramural Research Program. I was appointed to that position. Almost immediately, afterwards Fred Goodwin became the Scientific Director of the Intramural Program, and I worked with him in that capacity for four years.

SB: I remember Bob Cohen very well.

ME: Then, in 1983 Jim Wyngaarden, who was the Director of the NIH, asked me to be the Acting Director of the Clinical Center. I ran the hospital of the NIH for about a year and a half, and also began to be a candidate for psychiatry chairmanships.

SB: So, what was your thinking regarding “it’s time to be a department chair”?

ME: I had the idea and ambition to chair a medical school department of psychiatry for many years. I don’t remember this, but I apparently told my wife when I was dating her that I was going to become a psychiatry chair. Ellen’s father was the Chair of Psychiatry at Cincinnati for twenty-five years. He was the first psychiatry chair in the United States to have psychoanalytic training.

SB: Is that right?

ME: Replacing John Romano.

SB: Oh, my goodness!

ME: John Romano, who had come from the Peter Bent Brigham Hospital, stayed at the University of Cincinnati only several years, and then went to the University of Rochester as Chair of Psychiatry, taking George Engel with him.

SB: And, what was your father in law's name?

ME: Maurice Levine. He trained in psychiatry with Adolph Meyer at Johns Hopkins, and then came back to Cincinnati where he had been raised. He then trained in psychoanalysis under Franz Alexander at the Chicago Institute for Psychoanalysis. Ellen's father built a very eclectic department of psychiatry, with diverse interests in the social and psychological sciences. And, so, it seemed like the right time for me. I was starting to get calls. Vanderbilt was the third chairmanship that I looked at. And, then, three or four years later, as I reflected on our move to Nashville, it turned out that I became a psychiatry chair within six months of the age that my father and uncle became chairs of departments of internal medicine.

SB: Ahh...interesting!

ME: So, I concluded that it might have been a psychodynamic phenomenon!

SB: Yes, unconscious at the time, but powerful enough to actually change your direction of life.

ME: That is true. We all became chairs at forty-two years of age.

SB: Is that right? Well, isn't that interesting? Taking just before we go on then with the chairmanship, can you pick out several of the research accomplishments that you are most proud of, or that you feel that are the most important?

ME: I think that the methodological experiments on neurotransmitter metabolism were quite important at the time. The body of work on the physiology and neurobiology of human eating disorders was also important. I also took part in the development of two significant animal models of diseases, Parkinson's disease and depression. I will describe those briefly.

SB: Right.

ME: In the middle of my NIH years, we made a serendipitous discovery that became an important model of Parkinson disease. We accepted the transfer of a patient who had developed a "catatonic state" after self-injecting a chemical that he had produced in a home laboratory. The patient was college chemistry major and was trying to synthesize meperidine. We realized that the patient had developed a severe Parkinsonian syndrome and responded to pharmacological treatments for Parkinson disease. We demonstrated that the patient had clinical biochemical evidence of extremely reduced brain dopamine metabolism. We treated and followed the patient for about a year with psychiatric and neurological care. Unfortunately the patient committed suicide. The autopsy showed almost complete destruction of dopaminergic cells in the substantia nigra. We wrote up this first reported case of MPTP neurotoxicity and included some speculation on the nature of the neurotoxic compound. The story

of the publication of the paper is interesting. It was rejected by the *New England Journal of Medicine* as being “a fascinating medical detective story, but of too limited interest for our readership.” It was sent back by *JAMA* for having too many authors. This annoyed us, because this was truly a project in which each author had played an equal and different role: research fellow, psychiatrist, neurologist, biochemist, neuropsychologist, and neuropathologist. As was our tradition at the time at the NIMH, the first author was the research fellow who worked on the project. It was then published in *Psychiatry Research*. Several years after the publication of the above report, we became aware that the same neurotoxicity had occurred to 5 men in San Francisco, who were intravenously injecting meperidine made in a home laboratory. My research fellow at the time, R. Stanley Burns, flew to California and convinced two of these individuals to come back with him to the NIMH and be worked up on our research ward. Dr. Burns is a neurologist who has subsequently become an expert in movement disorders and a recognized neuroscientist. These individuals had the same clinical and neurochemical findings as the first patient.

SB: It was the same story; they were trying to synthesize Demerol?

ME: Yes. We were able to confirm our theory about what the neurotoxic compound was. Among other approaches, we had some glassware and reagents from the home laboratory of the first patient, which gave us, trace amounts of material to analyze by gas chromatography-mass spectrometry. We synthesized large enough amounts of the compound, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or MPTP, to conduct pharmacological studies. We eventually discovered that the compound, administered intravenously, produced a permanent Parkinsonian syndrome in non-human primates, but not in rodents. It later became clear that the neurotoxicity occurred in species that have a pigmented substantia nigra. This paper defined the MPTP primate model of Parkinson disease that has been used widely in etiological and therapeutic research. By the way, we did not have trouble publishing the subsequent papers in this sequence of research. The paper describing the neurotoxic animal model of Parkinson’s disease was published in the *PNAS*. Each of these papers, including the paper rejected by the *New England Journal*, has been cited well over 1000 times in the scientific literature.

SB: And, that animal model has become an important tool in neuroscience, which is still being used.

ME: Yes. And, the second model that I referred to was a very long collaboration with Bill McKinney and Dennis Kraemer who were at the University of Wisconsin and the Harry Harlow Primate Laboratory in Madison.

They were working on the neuropharmacology of the maternal separation model of depression in rhesus monkeys. This behavioral research was originally pioneered by Harry Harlow, a distinguished psychologist. McKinney and Kraemer were both senior, well-recognized investigators when we started our joint studies on the neurochemistry of this model of depression. Several striking findings have emerged from these studies. First, the *in vivo* indices of brain neurotransmitter metabolism that we used revealed selective abnormalities in the noradrenergic system. This is a finding that is consistent with the catecholamine hypothesis of affective disorders. Second, maternal and peer separation paradigms early in the life of a rhesus monkey produce changes in brain metabolism of catecholamines that last into adulthood. Challenge tests in adulthood, such as administration of amphetamine, produce distinctly different central nervous system catecholamine responses and behavioral responses. Thus, this may be a model of how early adverse experiences in affective development and bonding may produce lifelong psychopathology, altered neurobiology, and also altered responses to psychotropic drugs.

SB: Good! Those are two very interesting animal models. So you looked around and decided on Vanderbilt; and you went there in 1983?

ME: 1984.

SB: 1984, okay.

ME: I went to Vanderbilt because it has an excellent reputation as a school of medicine, and it is also a very powerful school in the field of clinical pharmacology. John Oates was a very influential and creative clinician-scientist at Vanderbilt at that time. He was the chair of my search committee. Subsequently he became Chair of the Department of Internal Medicine. Vanderbilt also had a very distinguished pharmacology department, and I had the opportunity to be a Professor of Psychiatry and Pharmacology. Vanderbilt had a good medium sized psychiatry department, previously directed by Mark Hollander, whom you may remember.

SB: Yes.

ME: A very scholarly physician, a psychoanalyst, and a distinguished psychiatric educator. The department had a modest research program. However, Vanderbilt also had a state hospital-based psychiatric research program called the Tennessee Neuropsychiatric Institute (TNI). It was similar to the Illinois State Psychiatric Institute or the Connecticut Mental Health Center, but on a smaller scale. One unique aspect of the program was that the annual budget from the state was shared between the Vanderbilt Departments of Psychiatry and Pharmacology. Fridolin Sulser and Elaine Sanders-Bush had their laboratories there. Tom Ban directed the clinical research program.

SB: They were all there when you arrived?

ME: Yes. In terms of history, the TNI was one of the first NIMH Clinical Research Centers. John Davis and David Janowsky began their research careers at the TNI.

SB: Right.

ME: When I went to Vanderbilt, I became the Director of the TNI, shared by psychiatry and pharmacology. I also had to reorganize the VA psychiatry service. I worked closely with Oakley Ray on that task. Oakley was the Chief of Psychology and the overall mental health program when I came. I briefly became Acting Chief of Psychiatry, and Oakley and I recruited a new staff of psychiatrists from academic medical centers. I recruited Peter Loosen from Duke to become the new Chief of Psychiatry.

SB: Excellent. Quite a group of ACNP members!

ME: Another major infrastructure project that I played a major role in was the construction and deployment of a for-profit psychiatric hospital jointly owned by the Hospital Corporation of America, which was a Nashville corporation, and Vanderbilt University. This project was controversial at the time, but worked out well. The Psychiatric Hospital at Vanderbilt, a 90 bed facility, was designed as a teaching hospital with conference rooms, faculty offices, and research space. It provided significant revenue to the Department of Psychiatry during most of my years at Vanderbilt.

SB: Very good. Your hospital was one of several successful partnerships between medical schools and corporate healthcare during the 1980's.

ME: Yes. With these three major infrastructure developments, we began to recruit new faculty. I established a division structure in the department with budget management responsibility. The divisions were in areas of specialized knowledge, clinical care, and research such as psychopharmacology, child psychiatry, alcohol and substance abuse. Some of the individuals whom I recruited, that are active in the ACNP, were Peter Martin, Rick Shelton, Bob Kessler, Herb Meltzer, and Ariel Deutch.

SB: A talented group!

ME: Early in my Vanderbilt years, I formed a strong liason with the Chair of Radiology, Everette James. We set out to establish a PET imaging program with an emphasis on neurochemical brain imaging. I established the neuropharmacology laboratories in our department. We jointly recruited Bob Kessler from the NIH to run the PET program. Bob Kessler and I had started to work together at the NIH on neurochemical brain imaging and we became very close friends. Bob and I then recruited Tomas DePaulis from Astra Pharmaceuticals to spearhead ligand development. We set up a partnership with PETNET Solutions, a small business in Knoxville,

TN, and started making isotopes and distributing them in Tennessee and Kentucky.

SB: And, selling them?

ME: Yes, to provide an additional revenue stream for the PET Center.

SB: Right!

ME: We eventually successfully defended two patents, for highly specific and potent dopaminergic and serotonergic imaging ligands.

SB: Okay, during this extensive career in research, you must have trained a whole cadre of clinician-scientists. Tell me about them.

ME: Well, I have had a strong educational agenda, like many of us have had who have served as clinical department chairs in medical schools. In my case, it was stimulating to have the opportunity to train clinician-scientists in clinical pharmacology who came from a variety of clinical specialties. So, just to mention some of them, Ron Kartzinel was originally Tom Chase's fellow, and he and I worked together when I assumed direction of the Section on Experimental Therapeutics. Ron moved to the pharmaceutical industry and eventually became the president of a pharmaceutical firm. Eric Cane, a psychiatrist, was one of my fellows, and currently is the Chair of Psychiatry at the University of Rochester School Of Medicine. Ronald Polinsky, a neurologist, was an early fellow when I was assuming leadership of the research ward at the NIH Clinical Center. He remained on the staff of the NIH in NINCDS for a long time, and then became the Director of CNS Clinical Pharmacology at Novartis. Walter Kaye, a fellow who focused on the neurobiology of eating disorders, also stayed on the staff of NIH within NIMH, and eventually became a Professor of Psychiatry at the University of Pittsburgh, School of Medicine, and more recently at UCSD School of Medicine. Dennis Langer was trained in medicine and law, and focused on pediatric psychopharmacology. He also became the president of a pharmaceutical firm. Peter Martin joined my section at the NIMH from the University of Toronto, and took a permanent position in the NIAAA Intramural Research Program. I eventually recruited him to be the Head of the Division of Substance Abuse in the Department of Psychiatry at Vanderbilt. Harry Gwirtsman became an expert and clinical investigator in eating disorders. After his fellowship at the NIMH, he returned to UCLA, and then joined the extramural staff of the NIMH. I then recruited him to Vanderbilt, where he has remained on the psychiatry faculty. Ulrich Tacke trained in medicine and psychiatry in Finland before he joined me as a fellow. He is currently a professor in Finland. Helmut Beckman was a fellow with Fred Goodwin, who trained in psychiatry in Munich, and worked with me in the laboratory. He returned to Munich and joined the distinguished Department of

Psychiatry at the University Of Munich School Of Medicine, eventually becoming the Chair of Psychiatry. David Goldman, whom we spoke of earlier, never left the NIH. After his fellowship with Carl Merrill and me, he joined the scientific staff of the NIAAA Intramural Program. He is now a Laboratory Chief in NIAAA. So, it was a good crew!

SB: And a distinguished group of children that you parented as a researcher. So, then you decided to take on yet another career.

ME: Yes!

SB: And, how did that come about.

ME: Well, it was very much like the chairmanship career. For many years, I had the aspiration to take a position that would give me a broader role in medical education at about that age. As a clinical department chair, you usually find yourself in the role of being an advocate for your own discipline. So, at a certain time at Vanderbilt, after about fifteen or sixteen years in the chairmanship, I began to look at deanships, associate deanships, and chief medical officer positions. I became one of two final candidates for medical school dean positions in four schools, and almost went to the University of Nebraska School Of Medicine where I was the leading candidate briefly. I found that I was encountering two issues. Because I was in the intramural research program of the NIH during my full time research years, I didn't have as extensive a grant history as other candidates. I also found that in the mid-west and in the south, there was some ambivalence about a psychiatrist running an entire medical school or a medical-surgical healthcare system.

SB: Really?

ME: Yes. I found that those attitudes were less evident in the Eastern United States.

SB: Interesting.

ME: Shortly before my move to Yale, I became more interested in chief medical officer positions, an administrative role that has matured in academic medicine in the last decade. These roles in teaching hospitals are usually combined with associate deanships.

SB: Exactly!

ME: And, that is how I happened to express an interest in your job at Yale and the VA Connecticut Healthcare System. When I accepted my current position, I was engaged in a deanship search where I was one of the final candidates.

SB: Oh, is that right?

ME: It was one of the smaller state medical schools, and I dropped out of the search. I was eager to be a member of the Yale medical faculty and a member of its distinguished Department of Psychiatry. And, I was also

interested in the VA Healthcare System as a model system for healthcare reform in the United States. I felt that I would learn a great deal and make a useful contribution by being a Chief Medical Officer in the VA. I also wanted to find a platform to make a broader contribution to medical education than was possible as a chair of a psychiatry department.

SB: Right. So, it is interesting how this comes full circle. It is interesting how your experiences in your very early life somehow influenced you along an entire career.

ME: I am looking forward to a long career in the VA and at Yale. Working until a ripe old age is also a family tradition.

SB: Oh, is that right?

ME: My father and uncle each retired at about the age of 80. My uncle entered the foundation world after retiring as a dean, and directed two different foundations. My father worked for 15 years at the University of Arkansas as a Distinguished VA Professor after retiring as a department chair. My father once told me that the best retirement plan is to keep working!

SB: Very good. Well, thank you very much! This has been a fantastic story and I really appreciate doing the interview!

ME: I also enjoyed the interview and appreciated the opportunity.

SB: Good enough, that was fun!

ELLEN FRANK

Interviewed by William E. Bunney, Jr.
Waikoloa, Hawaii, December 11, 1996

WB: I'm Dr. William Bunney, Professor of Psychiatry at the University of California, Irvine, and I'm interviewing Dr. Ellen Frank,* a Professor in the Department of Psychiatry, University of Pittsburgh. Dr. Frank is a leading clinical neuropsychopharmacologist. I wonder if we could start with you telling me a little bit about your training.

EF: Well, there is sort of an informal answer to that question and a formal answer to that question. Formally, I have a PhD in Psychology from the University of Pittsburgh and I had the sort of standard clinical psychology training offered in the seventies, but I think my informal training was probably every bit as important. I am the daughter of, I believe, a brilliantly talented social worker who was one of the founders of the discipline of geriatrics, and one of the first people to recognize the problems of older individuals as different from those of younger persons, perhaps because she was originally trained as a human biologist and worked as a laboratory technician before entering the field of social work. So, I had a kind of informal training all the years I was growing up in my mother's home. Then, when Tom Detre and David Kupfer first came to the University of Pittsburgh, I was hired to be their research assistant. They were working on a project in which they were trying to write a primer for the initial interview in psychiatry that they titled *The First Encounter*. The way we worked was that I'd come to the Institute a couple of nights a week and sit down and listen to the two of them talk about the diagnostic interview in psychiatry. I'd take notes, write the stuff up and I'd bring it back the next day. But, what it really was was a nine-month seminar in psychiatric diagnosis with two teachers and one student. So, a lot of my training really came in an informal way by listening to them and, then, later on, by watching how they did research.

WB: What about college and other training?

EF: Oh, that! Well, let's see. I have a BA. in drama from Vassar College in Poughkeepsie, New York, and a Master's Degree in English literature from Carnegie-Mellon University in Pittsburgh: very important to neuropsychopharmacology.

WB: OK, what created your first interest in neuropsychopharmacology?

EF: Well, growing up in Pittsburgh, I honestly didn't know that there was such a thing as a psychiatrist who wasn't a psychoanalyst until Tom and David

* Ellen Frank was born in Pittsburgh, Pennsylvania in 1944.

and the New Haven crew came to Pittsburgh. I had no idea that there was a *science* of treatment in psychiatry, but I became immediately fascinated by what they were doing. This was in the mid-1970s, when we first had what appeared to be highly effective treatments for depression and other major psychiatric disorders, and models for testing the efficacy of these treatments in an experimental way. I was just completely captivated by this idea.

WB: What were the drugs that they were working on at that time?

EF: For depression, amitriptyline and imipramine, and for schizophrenia, the standard antipsychotic drugs. I also was fascinated to see that some of these drugs might treat something that the family therapists had been trying to convince us was purely intra-familial, such as the Tourette syndrome. We certainly have a different idea about this now, but that these major drugs could actually have an effect on something like the Tourette syndrome was a completely novel idea at the time. Those were the main compounds that I got to see in action.

WB: You've done some really outstanding clinical work. Tell us about the research that you've done. Just give us a little history of the research that you've done.

EF: I sort of came into this by the back door. My expertise was really in the psychotherapeutic treatment of depression and, actually, post-traumatic stress disorder as well, that we did not call post-traumatic stress disorder in the mid-1970s. My first research grant, which I got as a second-year graduate student, was on the treatment of rape trauma which no one, then, was calling PTSD. I learned a lot in doing that study about how to do a controlled treatment trial of psychotherapy. So, when our department decided that a really important problem was the maintenance treatment of recurrent depression, I was asked if I would organize the monitoring of the psychotherapy part of that study. Well, as time went on, my role expanded and expanded and by the time the study was done, my responsibilities included running the clinic in which the study was being done and, finally, running the study itself. The question that the study set out to address was whether we could find better methods for preventing new episodes of depression in individuals who had well-established histories of recurrence. Previous studies, notably that of Prien and colleagues, had demonstrated that active medication, particularly imipramine, was certainly better than placebo and that a tricyclic antidepressant was considerably better than lithium for preventing pure unipolar depression recurrences. But, if you looked carefully at the outcomes from the Prien collaborative study, you saw that even the best treatment wasn't that good. About half of the patients were ill again at

the end of two years. So, our idea was that if you added psychotherapy to pharmacotherapy, perhaps, you could have a better outcome. What we also questioned was, whether decreasing the patient from an effective acute treatment dose to a so-called 'maintenance' dose was the best strategy. We had the impression that probably it wasn't. So, we elected to study a group of patients, all of whom had had acute treatment with drugs plus psychotherapy, i.e., imipramine and interpersonal psychotherapy, and then randomly assign them to the combination of drugs and psychotherapy, pharmacotherapy alone, psychotherapy alone, or a monthly clinic visit with no active psychotherapeutic or pharmacotherapeutic intervention for a period of three years. What we found was that if you continue active imipramine at the same dose that was used to treat the acute episode, you have a highly effective means of preventing recurrence, even in patients who, on average, are having episodes every year and a half to two years. What we didn't see was any added benefit for psychotherapy in addition to what might be termed 'full-dose' pharmacotherapy, but I think, frankly, that's because we had such a good outcome with the pharmacotherapy. There was really no room to see an added benefit. What we did find, interestingly and quite surprisingly, was that monthly sessions of the depression-specific psychotherapy had statistically significant protective effect, not as good as continued medication, but certainly better, clearly better than just monthly visits with no psychotherapy. Gerry Klerman used to say it wasn't a fair test because we used the highest dose of antidepressant and the lowest dose of psychotherapy in any trial ever conducted. But we clearly found that continuing an antidepressant at the same dose that gets the patient well, probably, keeps the patient well.

WB: Now, what impact do you think this has had, because this has clearly been supported?

EF: When I go around now and I do grand rounds and I meet with first and second year residents and they have the idea that the way to keep recurrent patients well is to keep them on their medicine, essentially, indefinitely, I feel that the message has gotten across. I think the study did two things. I think it served to reinforce a changed idea about unipolar depression and that is that it's a life-long disorder. I think that prior to the Prien study and our study there was the impression that schizophrenia was a life-long condition, bipolar disorder was a life-long condition, but unipolar depression happened in these isolated episodes and we didn't see it as something that really required maintenance treatment. And, I think that attitude has changed.

WB: And, that's a change.

EF: I think so. I think so. I haven't been in this field long enough to have the whole history, but it seems to me to have been a change.

WB: And what were your hypotheses in this work?

EF: Well, our hypotheses were that the combination of pharmacotherapy and psychotherapy would be better than pharmacotherapy alone, but we didn't show that.

WB: But others have, I would think?

EF: Well, no, not really. There's yet to be, either, an acute or long term maintenance trial that shows definitively that the combination is better than maximally effective pharmacotherapy. You can show that the combination is better than psychotherapy alone, but there's yet to be a study that shows that adding psychotherapy improves on maximally effective pharmacotherapy when your outcome measure is the proportion achieving a remission. Now, we've been looking at some of our own data and these are not controlled trial data, these are historical controls, patients in earlier studies, who got the combination, compared to patients in current studies, who are only getting psychotherapy or only getting pharmacotherapy and it does look like there is a slight advantage, not a huge one, a slight advantage for the combination. But, no one has yet pitted these treatments against one another in a big trial and shown an additive effect.

WB: Now, who were the major people, nationally and internationally, in this field that you've interacted with as part of your research network?

EF: Well, Tom Detre was a huge influence in my life. He was the person who showed me that this was a science, who had enough faith in me to ask me to write a grant as a first year graduate student, and, then, give me the support to do it. David Kupfer was huge influence in terms of teaching me ninety percent of what I know about how to set up and run and analyze a controlled trial. Myrna Weissman was an enormous influence because Myrna taught me that you could, and this was very important to me, that you could be an extremely serious scientist and retain your femininity. I can still remember the first time I heard her give a talk. I was just a lowly research assistant at Western Psychiatric and she arrived to give a research seminar in this diaphanous summer dress with that halo of blond hair, stood up and gave a perfectly organized talk and, then, responded to questions just with millisecond latency. And I thought, this is what I want to be when I grow up.

WB: A role model.

EF: Absolutely. But, I think we often miss to understand why it's so hard for women in this field. We so rarely saw, up there in front of us, a "like other" woman, doing what we would like to be able to do someday. And my daughter describes this experience when she was a second year law

student at Harvard, seeing a petite, dark-haired, dark-eyed *woman* up there teaching a law class. And, it was like a light bulb went on: I can do this.

WB: Well, where is your daughter now?

EF: She's an Assistant Professor at Marquette Law School. But, I think that that visual impression of a "like other," doing what she wanted to do was so important. There's, just not enough of these around.

WB: OK, any other people who are important?

EF: Gerry Klerman was very important because he was the one who really taught me, and I sort of did not know, that psychotherapy research hadn't been about *outcome*. I couldn't understand why anyone would want to study anything other than outcome; I really didn't understand that. This was a new idea. And, I think I learned a lot about research design from just looking at studies that Gerry had designed.

WB: He was good at that.

EF: He was good at that. He had so much foresight in terms of what the important problems were. When you look at his first depression treatment study, it was a continuation treatment study. He already recognized that, he knew in the 1960's that this was a chronically recurring disorder and the issue was relapse and recurrence. So, he's been important. Those are the main people. They're all familiar, aren't they?

WB: Now, you mentioned the issue of a role model, a woman, female role model, but I know you've had interest, over the years, in the gender issue here. I mean, it's obvious that this is a factor in depression. What has been your real involvement in that?

EF: Well, because I graduated from a woman's undergraduate institution that has always been, in its own way, a feminist institution, just at the time that the feminist movement was beginning to, or the second feminist movement was beginning to take place. And, I came back to Pittsburgh from college and within a couple of years I was hosting a talk show on women's issues, which I did for seven or eight years.

WB: I didn't know.

EF: So, in that program, for seven years, I addressed a whole range of topics that had to do with women and women's concerns. So, naturally, in any field, in which I would have found myself, whether it had been psychology, psychiatry, literature, you name it, I would have been interested in the question of gender differences and how women are different from men and how their experiences differ from the experiences of men. I spent my sabbatical last year, primarily, trying to figure out why it is that women are so much more vulnerable to depression than men. I've not found the answer, but it's something I've been interested in.

WB: Did you come up with something?

EF: Well, I have some ideas about why rates of depression take off so rapidly for adolescent girls, relative to boys. And, I think it has to do with the interaction between biologic and social factors in the age period, let's say, between ten and fifteen. But, it's too long a story.

WB: Now, in your research, are there new technologies, new instruments, new things that you had to develop in order to move it along?

EF: Well, I was part of a group, nationally, that became interested in specifying treatment delivery and, I think, part of that came from the idea that if we were going to compare psychotherapists across individuals, that we needed treatment manuals, that we need to be specific about how the treatment was supposed to be done. But, I think that also led to a specification of how pharmacotherapy should be delivered. I always like to say that we won't have the pure test of the pharmacotherapy efficacy until people can go up and get the active medication or placebo out of an ATM machine, that there's always the human factor in the delivery of pharmacotherapy and it has a big effect. So, I think an important set of tools for me were all of these manuals and treatment strategy descriptions that enabled us to do, what I think, were relatively well-controlled studies of the differences between pharmacotherapy and psychotherapy. Those tools enabled us to demonstrate in our long-term maintenance trial that the therapists who were supposed to be doing psychotherapy were really doing psychotherapy and the ones who were supposed to be delivering just medication clinic support, that's all they were doing.

WB: So, it was sort of a codification of what needed to be done?

EF: A codification of the interaction between the patient and the clinician.

WB: Do you remember when your first paper was published?

EF: I know when my first important paper was published. In 1978, I published a paper, based on an old data set that David Kupfer and Carol Anderson had brought from New Haven to Pittsburgh. It was on the differences between couples who sought marital therapy and couples who sought sex therapy. And, then, Carol and I went out and gathered a population of happily married couples, couples who felt their marriages were working, and demonstrated that sexual dysfunction, as defined by Masters and Johnson, was pretty much rampant in these happily married couples. That paper appeared in the *New England Journal of Medicine*, which isn't bad for starters.

WB: Pretty good.

EF: They tortured me over it. You know, every word had to be rewritten.

WB: Do you remember your first scientific presentation?

EF: Ah, yes. My first scientific presentation was based on this data set from New Haven and it was at the American Psychiatric Association in May of 1975. I'd never given before a scientific paper. I had no degree. I hadn't begun even graduate school. I felt like a complete and total fraud. But I was a good enough intuitive psychologist to know that behavior rehearsal was an important part of settling yourself down, so I went to look at the room and stood up on the podium the day before my presentaton. It was pretty...

WB: ...awesome, to say the least.

EF: Yes, but I got through my paper and nobody asked me any questions that I couldn't answer, so, if I was a fraud, they didn't know.

WB: What are you doing now? What is your current research involvement?

EF: Well, the questions really haven't changed very much. The T-shirt still says, "How Do You Prevent Recurrence?" I've become passionately interested in and concerned about manic-depressive illness and how poor our treatments are for manic-depressive illness, relative to our treatments for unipolar depression. So, I'm currently doing a study where we're looking at whether the combination of pharmacotherapy and psychotherapy, a psychotherapy that we've developed which we think might address some of the etiopathology of bipolar disorder, based on interpersonal psychotherapy, adds anything to the efficacy of well done pharmacotherapy in the prevention of new episodes of bipolar disorder. As I mentioned it before, in our unipolar study we really couldn't show added benefits for the combination of medication and psychotherapy, because even the drug alone-treated patients had very good social functioning, but bipolar disorder may be different. We're also doing a study that is another kind of follow-up to the original maintenance study. In that study we showed that monthly sessions of interpersonal psychotherapy had some protective effect. So, we asked ourselves who would want non-pharmacologic maintenance, given that pharmacologic maintenance works so well. The answer we came up with was women in the childbearing years, because there's a whole period when women are trying to conceive, carry and nurse a child when, generally speaking, all things being equal, you prefer not to be putting drugs into the system. So, we've been doing a study in which we are treating women acutely, with interpersonal psychotherapy alone and, then, randomly assigning them to weekly, bi-weekly and monthly maintenance IPT sessions, trying to do sort of the dose-response study of maintenance IPT. We're about four years away from finishing that one, so it'll be a while before we know the answer.

WB: Interesting. Are you using any of Beck's ideas in that study? He has his own approach to non-drug therapy.

EF: No. I actually started out very much as a cognitive therapy advocate. We used cognitive therapy in my original studies of rape trauma. I was trained to do CBT by Marika Kovacs who was a direct ‘descendant’ of Beck. When I first learned to do CBT, I thought I’d found the Holy Grail. I was very skeptical of IPT, because it seemed like a very soft treatment by comparison. That’s what my mother did. Not that I didn’t respect what my mother did; I just didn’t think it treated depression. Well, IPT is a very, very effective treatment. So, I’ve stuck with it; I’m an empiricist. I’ve stuck with what seems to work. And, I found that once you stop either drugs or psychotherapy the effects of these treatments dissipate rapidly. We found that with psychotherapy it’s quite possible to do maintenance or booster treatment. But, I don’t think these treatments inoculate people against recurrence.

WB: Would you pick one of your findings, discoveries as the most important one? Is that possible?

EF: Well, you know...

WB: The biggest contribution?

EF: Well, I think the first long-term maintenance treatment study of which David Kupfer was the original PI in which we demonstrated that there is a huge difference in terms of risk of recurrence between being fully treated and not being treated. That, so far, I think, is our major contribution. I hope we’ll get to build on it.

WB: Are there times when you’ve been tempted to leave the field?

EF: Not for a minute. I wake up every morning and I can’t believe that someone is going to pay me to do what I’m going to do today. Are there new questions I’d like to answer? Yes. Do I feel frustrated? The studies I do take nine and ten years. Do I feel frustrated when I think about the fact that I can only do two or three more of these in my life? Sure. But, nothing has tempted me since I found this. It is like finding true love.

WB: I guess the answer is that you’re happy with how things have turned out?

EF: I feel I’ve been very, very fortunate in terms of the kind of research environment that I happened to be in, to have had the kind of support that I’ve gotten from, not just from David and Tom, but from my colleagues and from the staff. Essentially, we still have the same research team that we had when we started the long-term maintenance study in 1981. So, I’ve been blessed by really dedicated team members who stick with us in this work. And, I’ve been blessed to have really wonderful relationships with people at the NIMH and they’ve been extremely helpful.

WB: All right, you’re a creative, imaginative person. I want you to think about the future, to think in the real world what would be ideally happening in

your field in the future, and in the blue sky world, what could happen up there, at some point, in the future?

EF: Well I think we're beginning to learn a lot from epidemiology about how these disorders progress and develop over the lifetime. I don't think, in my lifetime, we will ever come to true primary prevention in psychiatry the way the bacterial disease folks think of primary prevention, but we may get to the place where we can identify the early signs of Disease A, which almost always leads, later on, to Disease B, treat Disease A in its earliest form and prevent B from ever happening. So, for example, we know that almost all of the women who by age twenty-five have major depression, had an anxiety disorder as a child. Now, it's an empirical question whether if we could address that anxiety disorder at fourteen or twelve, we could prevent that person from ever going down this path. That would be something I'd like to see us do. I think we're on the edge of an explosion in terms of new compounds to treat depression. I think the SSRI's are just the beginning of a whole new range of treatments. But, I'm wondering whether we don't need to learn whole new ways of giving these medications. We've been giving them as though they were tricyclics. I hope there will be people who will step back and say maybe this isn't the way to use these compounds. They clearly have an impact, but maybe there's a whole other treatment strategy that we ought to be looking for. Maybe the model that worked with respect to imipramine and amitriptyline for the prevention of depression doesn't work at all with these medications.

WB: You're talking about frequency, dosage?

EF: I'm talking about frequency and I'm talking about dosage. The idea with the tricyclics is pretty clear that you take the person up to the maximally tolerated effective dose and just keep them there; but, maybe with the SSRI's, we need to start much lower and shift as treatment goes on. I think something may be happening over the course of time with these new drugs that the patient who's successfully treated, initially, with 10 mg, let's say, of fluoxetine, may need 20 mg to be maintained. So, I think, we don't really understand, yet, exactly how this works. We may think we know how they work at the receptor level, but what I'm interested in is what happens in the clinic. And, I think, as more and more of the treatment of the psychiatric disorders is being handled in the primary care clinics, we'll need even crisper models for how to use these drugs, because physicians don't have the time.

WB: That's another problem.

EF: I don't really have a clear understanding of all of what's going on in molecular biology, but I think it's not inconceivable that there may come a time

when you can ask the question, would you wish that there was no manic-depressive illness. I think Kay Jamison has really raised that question in a very effective way. Would we want a world in which there were no more people with manic-depression? I think the answer is probably “no.” Would we want a world, in which no one had schizophrenia? I think the answer is probably, “yes.” Will there come a time when we can identify in these diseases in utero and alter things *in utero*? Would we choose to do that? These are not just scientific, but big moral and ethical questions.

WB: They may not be that far away.

EF: That’s exactly right and the ethicists better get their act together, because we’re going to be pounding at their doors.

WB: Are there things I’ve left out, things that you want to put on the record?

EF: No, other than I would like to say that I kind of got here by accident. I had good library and writing skills. This crew, Tom and David and Carol Anderson, came from New Haven to Pittsburgh and were looking for somebody who could read and write and fix up their manuscripts. I came in completely by accident. This is the most unplanned thing. It feels like a perfect fit. I feel incredibly fortunate to have gotten here. I do think about how my life would have turned out, otherwise. I was an undergraduate drama student; I spent a summer in Stratford-upon-Avon. That summer the Royal Shakespeare Company was doing both *The Jew of Malta*, and *The Merchant of Venice* in repertory. Eric Porter was playing both of these roles so I got to know him a bit. About seven years later, Porter was being interviewed by Alistair Cook on Masterpiece Theater during an intermission in the *Forsythe Saga* and Alistair Cook asked him if he thought he’d been a success and he said, “Absolutely. I figured out what I want to do and I found a way to get paid for it”.

WB: Good.

EF: And, in that sense, I feel like a success.

WB: Well, you sound like somebody that’s in the middle of her career. You’ve got twenty good years of productive research that you’ve already put in and, probably, another x number of years to go in the future. OK, anything else?

EF: I don’t think so.

WB: OK, I’ve been interviewing Dr. Ellen Frank, a Professor at the University of Pittsburgh, whose unique contributions to the field of neuropsychopharmacology are internationally recognized. It’s been an honor to talk with you.

EF: Well, an honor for me, too.

PETER GASZNER

**Interviewed by Andrea Tone
San Juan, Puerto Rico, December 15, 2004**

AT: We're at the 2004 Annual Meeting of the ACNP, my name is Dr. Andrea Tone, and this morning I have the pleasure of interviewing Dr. Peter Gaszner.* Thank you for agreeing to be interviewed.

PG: It is my pleasure to be here.

AT: Tell us a little bit about your background and upbringing and how you got interested in medicine.

PG: Are you interested in my personal background or in my research activities?

AT: Both.

PG: Both, OK, let's try. As you know I'm from Hungary. It had a great impact on my life that in 1956 I was involved as a young soldier in the uprising against the communist regime and Soviet occupation. I was 18 years old at the time of the revolution and when I graduated from high school it created difficulties for me to continue with my education. My father was a physician and he wanted me to continue with my studies. He was not determined that I become a physician, because he thought that the life of a doctor was very difficult, but he thought I should study whatever I was interested in

AT: What did you want to be before the revolution?

PG: I wanted to be a chemical engineer. It's very interesting to think back, because I am a clinical psychopharmacologist now. In some way I returned to my first love. Of course, I am a psychiatrist first. To make a long story short, eventually I entered medical school in Debrecen, a city in Eastern Hungary, a very attractive university town. As soon as the "communists" found out that I entered university, they tried to have me kicked out from medical school. You might have heard that after the revolution we had a few very rough years with lots of punishments, executions and so on. As time passed, life became a bit easier. It was my good luck that I was able to continue with my studies, and, finally, in 1963, graduate from medical school.

AT: Can I stop you for a second? This is a really fascinating story that I think people will be interested in. The Communist Party and their representatives, actually, went to the medical school, or what happened?

PG: Yes, they did. It was a very difficult period of my life and it continued to be rough even after I got my diploma. There was an opening in the department of psychiatry at the Medical School in Debrecen, and the

* Peter Gaszner was born in Békéscsaba, Hungary in 1939.

chairman was ready to hire me, but I could not get the appointment, and not only because my past, but also because I was not a member of the Communist Party, or of the Young Communists Organization. Fortunately, the Chairman of the Department of Psychiatry at the Medical School in Pecs, a city in Southern Hungary, made it possible for me to become a resident, first, and, later, a psychiatrist in his department. After completing my residency I got my certification first in neurology, then in psychiatry, and later on also in clinical pharmacology. It was not possible to get a diploma in clinical psychopharmacology in Hungary, in those years. It was a great disadvantage for me that I did not join the communist party. To compensate for it I had to work very hard.

AT: But, they didn't pursue you, or try to kick you out of the field? They left you alone?

PG: No, I was able to get my PhD in Pecs and move to the National Institute of Neurology and Psychiatry of Hungary, in Budapest. I have been with the Institute now for about 25 years. I also received my Doctor of Science degree from the Hungarian Academy of Sciences and became the first psychiatrist appointed to a committee of the Academy. The Hungarian Academy of Sciences is a 150 years old prestigious institution.

AT: Can you tell us a little bit, to sort of set the stage, what psychiatry looked like at this time? Can you tell us what it meant to be a psychiatrist, the role of biological psychiatry within psychiatry and how other doctors viewed psychiatry?

PG: Hungarian psychiatry was prevailingly biological. It had strong ties with the German school of psychopathology. But, 70 or 80 years ago, before the Communist regime, it was also inspired by Freud and we had several excellent psychoanalysts. Many of them immigrated to the United States before World War II. Psychiatry was transformed during the communist regime. It was entirely biological. Psychotherapy, I don't know why, was prohibited in those years.

When I was young, as I told you, I was dreaming about to become a chemical engineer and after I became a psychiatrist, I tried to realize my dream by becoming a clinical psychopharmacologist. I was one of the first clinical psychopharmacologists in Hungary, and the founder of the Hungarian Association of Psychopharmacology. Later, I became also the founder of the Journal of the Association. By now *Neuropsychopharmacologia Hungarica* has become an international journal. Although I'm a psychiatrist and psychopharmacologist, I'm combining pharmacotherapy with psychotherapy in my practice. I'm the head of a psychiatric service at the National Institute of Psychiatry and Neurology of Hungary. It is the largest clinical service with 140 patients at the Institute and also in Hungary. My

service is designated as the psychopharmacology service of the Institute. Yet, I spend most of my time at work doing psychotherapy.

AT: I didn't know that.

PG: I believe that pharmacotherapy together with psychotherapy works better than pharmacotherapy alone.

AT: So, biology can be enhanced in tandem with an emphasis on environmental inputs?

PG: Exactly. Our patients with major depression or schizophrenia are treated with a combination of pharmacotherapy and cognitive therapy.

AT: So, someone with panic disorder would get exposure to psychotherapy at the same time that they might get an anxiolytic.

PG: Yes. Panic disorder is one of the common diagnoses in Hungary these days. We are treating patients with panic disorder with serotonin uptake blockers together with psychotherapy. I have a feeling that all of our patients respond favorably to our combined treatment.

AT: That's wonderful. So, just for the record, I want to make sure that people, who are viewing this videotape, get this correctly; you are working at the National Institute of Psychiatry and Neurology of Hungary?

PG: Yes. I am 65 years old and intend to work three or four more years before retirement. I like very much what I'm doing.

AT: That's good. Tell us about some of the earliest work that you did and take us through your career, what you see as the key contributions that you've made to the field.

PG: Are you asking me about the clinical research I did?

AT: Right.

PG: It might be interesting to have it on record that I did my research always at nights because during the day I was busy attending patients. During the day we have to do our clinical job because in Hungary because we are very short of psychiatrists.

AT: Could you get funding from the government for your research? Probably getting funding from industry wasn't possible.

PG: No, I could not get funds from the Hungarian government. The Hungarian government was always very poor never had funds in the communist era, nor in the past 15 years. The democratic government we have in the past 15 years does not spend enough money for the health service. The entire health service, and, especially psychiatry, is under-funded. To do research, I had to collaborate with colleagues in the United States, Western Europe and Eastern Europe. Usually the money for the research is coming from the United States and Western Europe.

AT: Going back to when you started your career and you're doing your research at night; I have this image of you by a tiny little lamp on

the table, which may be misleading. What were the kinds of questions you were most interested in and how were you able to do your work?

PG: I was involved in six different areas of research. Chronologically, I was interested first in atropine coma therapy in psychotic, and especially schizophrenic patients. It is a treatment modality that is no longer in use. But about 35 years ago when we still did not have effective drugs for treating psychotic patients, it was very useful.

AT: Was chlorpromazine available to you in Hungary?

PG: Today, every drug is available in Hungary.

AT: But in the late 1950s and 60s?

PG: We had chlorpromazine, but not as much as we needed. To be able to do our job we had to use ECT and atropine coma therapy. Atropine coma therapy was effective and had virtually no side effects. Atropine was given intravenously. One of the difficulties of atropine therapy was, and I found this out early in my research, that patients widely varied in their sensitivity to the substance. For some patients I had to administer as high as 1,000 mg of atropine sulphate to induce coma, whereas for some others 10 mg was sufficient.

AT: If I understand what you're saying correctly, this was a method you pioneered as an alternative because of the political reality of not being able to get enough antipsychotics. Let me ask you: Did you continue to use it, even after the new drugs became available?

PG: When I transferred to the National Institute in Budapest some 25 years ago I stopped using atropine coma therapy. By then we had enough psychotropic drugs in Hungary.

AT: OK, that's what I was wondering.

PG: But truly, we never really had enough money to pay for psychiatric drugs. Western pharmaceutical companies gave us drugs free of charge in the hospital.

AT: How did you get them?

PG: Representatives of the companies came to see me in my office at the Institute, and, offered their drugs.

AT: So, even under Communism, the companies were allowed to have offices in Hungary? This is very interesting.

PG: Yes, it was a very interesting situation. If we hadn't been given drugs free, we wouldn't have been able to treat our patients. This is the situation even today. The new atypical antipsychotic drugs are extremely expensive. We can't afford to pay for them. But if we can get them free of charge in the hospital, we can use them treating our patients.

AT: In hospitalized patients?

- PG: Yes, and after discharge the patient can continue on the same drug. That is good business for the drug companies.
- AT: Right. That's very interesting. Sorry, I interrupted you. You were saying you had six different projects and we were talking about the first.
- PG: In 1979, I went to England to work in Manchester with Sir David Goldberg and Professor Elemer Szabadi in clinical psychopharmacological research. I was involved in the development of a new method to study the peripheral effects of antidepressants and neuroleptics with the employment of psychophysiological tests, such as pupillometry, galvanic skin resistance, and others. Then, in the 1980s, I went to work with Tom Ban in Nashville. I was there for the first time in the mid-1980s for six months, but I kept on going back every year after that until the mid-1990s.
- AT: This was at Vanderbilt?
- PG: Yes, it was at Vanderbilt in Nashville. I was working there also with Mike Ebert who moved since that time to Yale. And, as you know, Tom Ban is now in retirement. I am very sorry that he is no longer in Nashville.
- AT: Yes, we all are.
- PG: With Tom Ban we worked on the development of a new polydiagnostic methodology.
- AT: The CODE system?
- PG: Yes, the CODE system, the Composite Diagnostic Evaluation System.
- AT: How does that differ from DSM?
- PG: The DSM, and also the ICD, is a classification in which diagnoses are based on the consensus of experts, whereas in the CODE the diagnoses are based on many of the different classifications in the past and present, including the DSM and ICD diagnoses. It gives a profile of the diagnoses included in the system. CODE-DD, the composite diagnostic evaluation of depressive disorders is based on 25 diagnostic classifications, and CODE-HD, the Composite Diagnostic Evaluation of Hyperthymic Disorders, I was especially involved with, is based on 16 diagnostic classifications.
- AT: I can't tell you the number of people who have sat in your seat, who have told me, during this meeting and at previous meetings that DSM is so flawed that it almost makes no sense to use it as a diagnostic tool and, yet, people do. Why aren't we all using CODE?
- PG: That's a very good question. Everybody is criticizing consensus-based classifications, but keep on using them. We also founded an International CODE Collegium, and a CODE Institute. I'm currently the president of the Collegium, and I'm also the Director of the Institute.
- I was also involved with the clinical development of reboxetine about 15 years ago. The drug was only recently marketed for the treatment of

depression. It was an Italian company that developed originally reboxetine. Then, reboxetine went to Kabi and recently it belongs to Pfizer. I have known from the beginning that it's a very effective antidepressant. Still it took many years before it was marketed and even now it's available only in some countries.

AT: That tells you a lot about how marketing and industry shapes what people prescribe and what patients receive.

PG: Exactly. Drug companies are concentrating more on their profit and less on new drug development.

Another area of research I have been involved with is clozapine, the first atypical antipsychotic. It was introduced about thirty-three years ago in Hungary and I have been using it since that time. It is my favorite antipsychotic drug. By now, I treated more than 1,000 patients with clozapine. It is the largest cohort of clozapine treated patients in one center in the world! Agranulocytosis is a very dangerous side effect.

AT: Tell us...

PG: From the more than 1,000 patients I treated we had only 2 patients with agranulocytosis and they are still alive. Of course, they are no longer on clozapine, but they are still alive. I believe it's genetically determined who will develop agranulocytosis. As you probably know about 35 years ago several clozapine treated patients developed agranulocytosis in Finland. As a result clozapine was almost taken off the market. But, luckily it was rescued. In the USA, Herb Meltzer is the leading researcher involved with clozapine and I have been collaborating with him for some time.

AT: I didn't know that.

PG: He's now at Vanderbilt in Nashville.

AT: Yes, he's been a big fan of history and this endeavor. Can you tell why there was a need for a new kind of antipsychotic?

PG: The main advantage of atypical antipsychotics is that they don't cause extrapyramidal side effects at regular doses. If we are using them in higher doses so, they may induce Parkinsonian manifestations and other CNS side effects.. Another advantage of atypical antipsychotics is that they don't cause suicidal ideation. I first learned this from Herb Meltzer. This is very important for me because for some time Hungary had the highest suicide rates in the world.

AT: I didn't know that. What time frame?

PG: In the 1980's we had nearly fifty suicides per one hundred thousand inhabitants, which was the highest in the world. Actually, the East Germans had higher suicide rates than we, but when they realized how high they suicide rate is they stopped doing statistics on suicides in East Germany. We had no single suicide in our clozapine treated patients. The drug seemed

to be even effective in suicide prevention. I also think that the danger of agranulocytosis is highly exaggerated.

AT: How do you explain the Finnish report?

PG: The Finnish and the Hungarian languages are related to each other but it must be a genetic difference between Finns and Hungarians with regard to clozapine induced agranulocytosis. Herb Meltzer and I thought that we should look into this matter and I might be able to answer your question sometime in the future.

AT: Do you think it might be genetic?

PG: Yes, I think so.

AT: I think we were up to four or five areas of your research.

PG: The area we have not covered as yet is social psychiatry. We are conducting a rather unique research project in social psychiatry. Let me give you the background to it. Hungary used to be a very large country compared to the Hungary of today.

AT: It was part of the Austro-Hungarian Empire.

PG: Yes, we lost the first and the second world wars and, because we lost the wars, we lost about two-thirds of our territory. Hungary became very small and lots of ethnic Hungarians are living in neighboring countries. In our research we are studying anxiety in the Hungarians who are returning to Hungary from Slovakia, Romania, Yugoslavia, and Serbia because they had difficulties living in those countries. The governments in those countries are not very friendly towards ethnic Hungarians. They are coming to live in Hungary without jobs, money, or housing and their life in Hungary might even be worse than it was in the country they left. Their anxiety is usually very high. Many of them become schizophrenic, depressed, or even suicidal.

AT: So, ultimately, this can be traced back to their response to this unique stressful situation?

PG: Yes. Hungary is a poor country. We have no money for refugees. We would like to improve their lives, but it has not been possible as yet.

AT: Did you, at any point in your career, think about leaving Hungary when it became possible to do that?

PG: Twenty-four years ago when I was working in Great Britain. I was invited to stay, but I did not want to live there.

AT: This is Manchester?

PG: In Manchester. The same situation arose in Nashville fourteen years ago when Tom Ban invited me to stay in Nashville and work with him. When Tom went to Toronto, he invited me to join him there to work with him, but I did not go. It is a curious situation, because life in Hungary can be very hard, but still I want to live in Hungary.

AT: Have you ever read the *Unbearable Lightness of Being*?

PG: No, I did not.

AT: A couple of final questions and, then, I'll ask you to add anything on. I interviewed at CINP, Eva, who practices psychiatry in Czechoslovakia.

PG: Are we talking about Eva Ceskova? She is s a very good friend of mine.

AT: Yes. She had a lot of interesting things to say about mental illness under Communism.

PG: Did she talk about psychiatric abuse?

AT: She mentioned a little bit of it but felt it was exaggerated.

PG: I went several times to Russia, and was aware of psychiatric abuse there. I also know of psychiatric abuse in some of the other Eastern European countries, but in Hungary we had no psychiatric abuse. Hungarian psychiatrists were always very honest. But even in Russia it was created by the Government and not by psychiatrists by declaring that people who are against the Soviet regime are mentally ill. It was not entirely the fault of Russian psychiatrists.

AT: When we talk about psychiatric abuse, how were people being treated when abused?

PG: ECT was the treatment of choice.

AT: Punitively, to punish them?

PG: No. Russian psychiatrists diagnosed dissenters as paranoid, because whoever was against the Communist government must have been paranoid. It was not a wrong diagnosis on purpose. Some honestly believed that this was the case.

AT: I understand what you are saying. What about patients who were schizophrenic, and not because they thought Communism was wrong, would they be treated, also, with ECT?

PG: Yes.

AT: But, were they properly treated?

PG: Yes, the Russians had problems obtaining psychotropic drugs; they had no money to buy them.

AT: And, western countries weren't allowed to set up offices in Moscow?

PG: I don't know.

AT: Let me ask you, what advice would you give someone who's new to psychiatry and they turn to you and ask you about ECT?

PG: I used ECT extensively thirty five-forty years ago, because we had no other treatment options. Today, ECT is quite popular again, but I am using it very seldom.

AT: Why?

- PG: Because drug treatment and psychotherapy work perfectly well in combination. I don't need ECT for the vast majority of patients; I am using ECT only for patients with major depression who don't respond to treatment
- AT: Now, someone like Max Fink would argue that we should do ECT instead of subjecting patients to more and more antidepressants.
- PG: Max is a friend of mine and he told me that ECT is dying and it is true.
- AT: Why?
- PG: We don't need ECT; we can treat patients with antidepressants and antipsychotics combined with psychotherapy. I have virtually no or very few treatment failures if I am using combined treatment with drugs and psychotherapy.
- AT: Do you think it maybe harder in the United States, in particular, for psychotherapy to be integrated into patient's treatment? Often, the doctors are writing prescription because they have five minutes only to spend with their patient. They're not going to be able to do psychotherapy.
- PG: That's a very good question. That's a problem. The doctor has no time for psychotherapy. They should have time so. The doctors on my service are doing psychotherapy. It is possible to do psychotherapy in fifteen minutes. We are also using group therapy. It is more economical.
- AT: Groups of four or five?
- PG: At least ten.
- AT: Here at ACNP, we have a lot of sessions devoted to smaller and smaller parts of the brain. If you think about the future, do you think psychotherapy will return out of necessity?
- PG: No. I don't think so. The future is in genetic research. In the future we should be able to examine patients, and based on their genetic make-up suggest specific drugs that will work immediately.
- AT: So, we don't need psychotherapy in the future?
- PG: We won't need psychotherapy in the future. Let me tell you about a patient I consider my greatest professional success. The patient was an economist. His mother was schizophrenic, his sister was schizophrenic and there were also other schizophrenics in the family. He was schizophrenic as well. First, I treated him with haloperidol, because we only had haloperidol at the time and he was not responding to treatment. Then, clozapine became available, and I treated him with clozapine. After a few weeks of treatment with clozapine he became symptom free. He has been on clozapine now for 33 years and during these years he has had no symptoms of schizophrenia. He got his PhD, then his DSc. He became first a respected teacher. Then he was appointed as chairman of the department of economics at his university. Today, he is the President of a university in Southern Hungary. About eight years ago, he told me

that his university would like to appoint him president but I told him at the time he should not accept it because it's a very hard job. He therefore refused the job at the time. But, two years ago, he was approached again and this time I told him, OK, and he accepted it. I consider it as the greatest success of my life.

AT: You have four children.

PG: Yes.

AT: One of them with my name.

PG: Of course, you know Andrea. Three of them are physicians and the youngest one started medical school, but changed her mind and went to study economics.

AT: Oh, that's wonderful.

PG: It happened because of her boyfriend.

AT: Men will do that to us; derail our best intentions. Do you have anything you'd like to add? This has been a wonderful experience.

PG: Thank you very much for inviting me.

AT: Thank you for joining us.

PG: Thank you.

AT: It was wonderful.

IRA D. GLICK*

**Interviewed by Donald F. Klein
Waikoloa, Hawaii, December 11, 2007**

DK: Why don't you give us a start and say something about your education, your early interests and how you got into this field? What were the steps?

IG: Well, the story is, my father was an old-fashioned family physician. I used to go around with him when he would see patients. I always knew I wanted to get into medicine, with a capital M. The main thing I noticed when I was with him that he would actually talk to, not only the patients, but also their families. So, in 1961 when I finished medical school, I went to New York Medical College, but the idea of managing patients with GI bleeding or being a surgeon and taking out organs I thought, was not for me. I didn't just want to become a technician. Actually, I wanted to get to know something about patients and about their illnesses. When I got on the wards in my internship, giving medicines was a lot of fun, but was also not fulfilling enough. I wanted to do more. So, I decided to go into a not-so-popular field, psychiatry, where I could both talk to patients and families using medicines. So, after Dickinson College in Carlisle, Pennsylvania, as an undergraduate, then New York Medical, by luck I chose to go to Hillside Hospital in Glen Oaks, New York, where you, Max Fink and others were teaching. At Hillside, my teachers were not just teaching me psychiatry, but taught me to think about how disease develops and how you treat them, i.e. a natural history of diseases. That's a long answer to a short question.

DK: That's quite all right. And, how did you get from there into research?

IG: During the first six months that I was at Hillside, I kept asking the questions; does this work, does that work, for how long, for whom? It just seemed like a natural part of working with patients and families. The families would ask, "Is this going to help, doctor?" That led to me asking the same questions of myself. As it happens, while we were at Hillside, you were running large controlled studies, working on different response patterns to antidepressants and other drugs, trying to figure out which drug for which patient. That's how I really got into research. I had done some research in college. I had done some research in medical school, and I kept asking the question, "why".

DK: So, what was your career track like? How did you initially get involved in research and where did you go from there?

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IG: Well, when I was at Hillside, I started writing up cases that were unusual, and one of the first cases I had was a guy who turned out to have Kartagener's syndrome. He also had schizophrenia, so that led me to a literature search. And that led to a paper about Kartagener's syndrome in schizophrenia; no one had reported that association before.

DK: You figured his mother didn't do...

IG: Right, as we thought about things in those years. It turned out, as it happened in that particular case, that the guy's brother got hospitalized the same week. He also had schizophrenia. That was an eerie coincidence. During that first year at Hillside, I also noticed that with female patients, their mental status, especially their mood changed and their illness, usually schizophrenia or mood disorder, fluctuated with their menstrual period. This led me to ask a question, a very basic question: "could hormones influence or change the course of a particular mental disorder?" That's how I got into it. And, I did a couple of research projects, while I was at Hillside. Then in the fourth year at Hillside, I think the other major influence was being Chief Resident. This administrative responsibility involved me setting-up the teaching program. That got me into teaching, and teaching got me into, "what's the evidence for what we're doing". Needless to say, during the time I was at Hillside, I was fortunate enough to be admitted into the ACNP at the early part of my career relatively speaking, when the organization was just getting going. The organization has been a major influence on me, not just from your mentoring, but there were a half a dozen people here, who were extraordinarily helpful to me.

DK: Can you name them?

IG: Dick Shader, Carl Salzman, Leon Epstein, Lou Lasagna, Phil May, Gerry Klerman, yourself, who mentored me along the way. They taught me to use the scientific method to get answers to the questions like "what is this particular drug doing with this particular person at what time in the course of the illness." This organization was crucial to pushing me along the research track from my earliest days in psychiatry.

DK: You moved on from Hillside, though.

IG: Well, as it happened, I got drafted. I went to Ft. Gordon, GA, where I started with the smallest psychiatric service in the south, two beds. But, they put me in charge of the service; the hospital kept expanding, expanding, expanding, and I ended up in charge of the biggest hospital in the South, two hundred beds with 12 psychiatrists. That led me to the next step in my career, because when I left the Army, I went to California where I had interned at Mt Zion Hospital.. Having been trained as a teacher and researcher, I went to UCSF in charge of an inpatient service. The ques-

tion was what do the hospitals do for patients post-hospitalization, and how it was whatthey did in the long run?

DK: Where were you in California?

IG: I went to the University of California San Francisco, at Langley Porter Institute. At that time, as fate would have it, Governor Ronald Reagan was emptying out the state hospitals to save money. I went there and noted the average length of stay, at that time, was about two or three weeks and I said, well, I “know” that the right hospital treatment is a longer treatment, I’ve come from the Hillside hospital, which hospitalized people six, nine or twelve months. Since the nurses and the hospital administration were fighting with me about wanting to keep patients longer, I thought what we ought to do was a controlled, random assignment study of the two different approaches. So, Bill Hargreaves and I designed the infamous “short vs. long psychiatric hospitalization study”.

DK: Short and long?

IG: At that time, around the United States, a short hospitalization was three weeks. A long hospitalization was three months. So we randomized patients into two groups. The hypothesis was, given the prevailing wisdom of the time, that patients who had a mood disorder, and would remit quickly, would need the shortest stay and the patients who had chronic schizophrenia or a personality disorder would need a longer stay. We “massaged” their personalities, gave them the medicine that they needed, saw how they reacted and we followed them for two years after the hospitalization. What we found was exactly the opposite of what we thought; that is, the mood disorder patients needed to stay longer, because when discharged had no idea that they needed medicine post-hospitalization. The patients with chronic schizophrenia and personality disorder mostly did not benefit from the longer stay. They did better with the shorter stay. And, in an interesting correlation, Phil May, at an ACNP meeting, opined that the patients with the mood disorder who stayed longer and learned about their illness while we worked with them and their families, realized there was something wrong and they had to take their medicine. In short, they had better medication compliance and that accounted for a better outcome. And, those who didn’t have a clue what was going on stopped their medicine and relapsed. So that was an important finding. This was one of the very first random-assignment studies in psychiatry. I have to say, again, I’ve been heavily influenced by what I learned at Hillside and at ACNP. Random assignment studies (RCTs) were becoming the gold standard for all of medicine.

DK: How long were you at UCSF?

IG: I was at UCSF for ten years. I was recruited back to New York to Cornell University Medical College. I was put in charge of the inpatient service at Payne Whitney, which was organized into five wards, run by psychiatrists with psychoanalytic training who had interest in doing hospital work. Their approach was quite different from mine. I tried to convince them with the unusual notion for them that we had to medicate people.

DK: That was when?

IG: In the 1970s and '80's medication for Axis I disorders was not accepted as it is today; it was still controversial, especially in a psychoanalytic setting. The second issue was that these medicines may be helpful but, as best as I can understand, unless the patients swallow them, they won't help. So, to achieve that with the severely ill patients admitted to the hospital we had to work with families and that was anathema at that time. The upshot of that was an NIMH grant, designed with John Clarkin, to study the effect of working with families in a hospital setting to improve outcome. So we did again a random assignment study. Both groups received good medication treatment. One group got the family intervention as well and the other group didn't. In this study we showed for most of these disorders we worked with, i.e., bipolar disorder, schizophrenia, depression, that working with families actually helped. What it did was improve medication compliance, which was the key mediating variable for improving outcome. I also conducted a random assignment study, not NIMH funded, of short hospital stay plus a transitional treatment program vs. directly into an outpatient transitional treatment program. There wasn't much difference in outcome. So, those were the second and third major studies that I did. Then I got involved with a large multisite study designed by Nina Schooler and Sam Keith. For me it was the next logical step. It was called Treatment Strategies in Schizophrenia (TSS). The background was that there were some patients with schizophrenia who took low doses of antipsychotics and did just as well as those with a standard dose. The drugs used were first generation agents (FGAs). EPS and TD was the main problem, so the notion was if you could lower the dose, you'd have less EPS. The hypothesis was that a lower dose, plus a family intervention, would give you just as good an outcome as the full dose. The upshot of that study was that you didn't have to medicate with a full dose of an antipsychotic to get a good outcome. There was no interaction effect. The family intervention did a little, but not enough to improve outcome.

DK: Was anybody else doing anything of that sort at that time, in terms of trying to be systematic about the question of would family intervention really help?

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- IG: There were very few controlled family intervention studies, except for ours and that of Mike Goldstein with Bipolar Disorder.
- DK: And, as I know not much progress has been made in that area of research.
- IG: Right. In terms of psychotherapy, there have been very few NIMH funded studies. There's the big NIMH individual psychotherapy intervention drug vs. medication alone study, but very little in the family therapy field. I think I'm the only one of the few to get NIMH funding for that kind study. Clarkin and I actually did another family therapy study when I was at Payne Whitney. That focus was on bipolar disorder. We developed a family intervention for spouses of patients with bipolar disorder. We randomized patients; one group received very good drug treatment plus family treatment; the other group received no family intervention. What we found in that study was, that family intervention was helpful for those who were very psychotic, i.e. for severe mania, it improved outcome in the population over one year. But for those who were less severe it didn't do much. But, again, that was a nice RCT.
- DK: It's interesting that studies of that nature haven't taken off.
- IG: I think the reason is that those interested in family research changed from psychiatrists to charismatic clinicians in social work, who are not interested in doing research. The one guy who's made a terrific career on that line of research is David Miklowitz. He was mentored by Mike Goldstein from ACNP, who was a very good mentor. Miklowitz has done RCT studies in depression and mania, NIMH supported trials which showed positive results by working with the family.
- DK: So, where else did you go from there?
- IG: After Payne Whitney, I got recruited to Stanford and focused my efforts, working with Alan Schatzberg, another ACNP member and former President. We set up a schizophrenia research clinic, which has thrived and been mostly psychopharmacology research. Most of that work has been presented here. When I moved from Payne Whitney out to San Francisco, one of the projects that you and I worked on, if you recall, was looking to introduce drugs used in Europe and Asia to the United States. I went over to Europe and Asia in the summer of 1993, and came back with a list of ten or twelve orphan drugs. Although very few companies wanted to invest and pick them up, I think it brought modest attention to the compounds that are being used in other countries. As it turns out, this lack of interest was part of a larger trend after the 1970's, as you mentioned in your talk earlier this week. Drug development really slowed down. We got all of these useful drugs in the 1960s and '70s and, then, there's been a gradual drop off.
- DK: I think you skipped over the time you spent in Washington.

IG: Right. The other interesting thing that I did was from 1988 to 1990 when I was a Science Advisor to the Director of the NIMH, Lew Judd, another long standing ACNP member. I went down there, really trying to push an agenda of increasing clinical drug trials. We tried to develop a new version of what Jonathan Cole had done years earlier in his branch, which got shut down. You were there at that time. I think we both had an agenda for doing large-scale controlled trials, which would be carefully designed and peer reviewed. It was a very fertile and a very stimulating couple of years that we had down there. I think, in part, it led to some of the larger trials that later developed, like Star-D, CATIE, etc. I like to think we had something to do with that. A lot of that methodology was talked about here. You know, no study is perfect. All these studies were done but I'm not sure they gave us useful data. I believe that the next steps need to be carefully thought out with psychiatric statisticians involved from the earliest design stages to make sure that you can get answers in order to advance the field. So, being the NIMH Science Advisor was an important step and, needless to say, ACNP members were prominent. Part of what we tried to do was to bring them into the ADAMHA and into the NIMH family.

DK: And, where did you go from Washington?

IG: I got back to Stanford in 1993 and have been doing controlled trials ever since. I've worked with virtually every new antipsychotic compound that's come to market, i.e. the second generation agents (SGAs), and I worked in the CATIE project. The most interesting upshot was the meta-analysis that John Davis and I did. John has also been a long-standing ACNP member. In the meta-analysis that we did, we compared the second generation agents to each other and to the first generation agents. What the data suggested was that there were some second generation agents that were better than first generation agents, particularly clozapine, risperidone and olanzapine. As for the rest, they didn't look much better than the first generation agents; although, they don't have the EPS and tardive dyskinesia.

DK: Remind me, was the meta-analysis you did with John Davis based on acute or maintenance studies?

IG: They were both acute and maintenance, long-term studies. It was every controlled study we could find, longer than six or eight weeks. They were studies from around the world.

DK: You got also involved in some areas of teaching?

IG: Right.

DK: And ethics?

IG: Right. As it happened, the first committee I was put on, when at ACNP, was the Education and Training Committee. I mentioned that while I was at Hillside, I got interested in teaching. When I was at UCSF, I taught a

course on Teaching Psychiatry, which the residents and young faculty loved. So, here at ACNP, Dick Shader, Carl Salzman, David Janowsky and I happened to be on the committee when the Travel Awardee program started. We received some funding to bring young investigators to the meeting. The idea being that the organization would die without new blood. To keep it vital, we needed to bring young people in. So, once we got the trainees in, the next question was what to do with them in addition to their simply attending symposia. So, we tried to set up a teaching program. One of the things they said was, not only was it difficult to do drug treatment in their institutions, this was back in the 1970s, given the psychoanalytic bias in the field, but there was no curriculum to do it. So we developed, in the mid 1970s, the first model curriculum in psychopharmacology. Just as it is crucial to know in research that randomized controlled trials are the gold standard, when you talk about curricula the crucial issue is that nobody wants to teach from anyone else's curriculum. The thinking is: "if I didn't develop it, I'm not using it". So, we developed this teaching tool. We had twenty or thirty lectures on the psychopharmacologic treatment of most common psychiatric syndromes. How did we do that? We got experts to give lectures, and we put it together as the first ACNP vetted publication. It was also the first model curriculum in psychiatry. The model curriculum was also the first ACNP official publication. Oakley Ray was very instrumental in seeing this through. We distributed it to residency training directors. At first, without any marketing, it hit like a lead balloon. It went to print and sat on people's desks. We realized that it wasn't enough just to print it. Our subsequent success led to four subsequent editions of the model curriculum. We're now into a fifth edition. We now have seventy lectures with over four thousand slides. We've forged a permanent link with US training directors to use the curriculum. We're going to be able to get it into most training programs around the country. We've been selling about a hundred to hundred and fifty copies of every edition, and sales have gradually risen. And, we're starting to get into Asia. We've gone into Japan and presented it in China. I went to Indonesia; it's being used there. We're working with CINP and ECNP to try to get it into Europe and it's been taken to Somalia, Israel and Chile in South America. It's now around the world. It started at ACNP and it's been a lot of fun and, unlike a lot of things that we do, it's actually been useful.

DK: Yes, the training directors, in particular, as I recall, originally were not thrilled about it. They felt you want to cut in on their turf.

IG: Exactly, for example, at one medical school in New York, they do a hundred lectures on psychodynamic psychiatry and ten lectures on

psychopharmacology, so why do they need a curriculum? So, it's been five years of working with the training directors, to get them to change their mental set to use the curriculum. So, that's been important. Then, two years ago, I put together, with Dave Braff, a session on how to ethically work with industry. There had been so much flack about working with industry, about conflicts of interest, that I decided to try to put together a session to speak to the issue. Could you work ethically and collaboratively with industry? It was a reasonable first effort in how to do this. It's a difficult problem, and I don't think there are easy answers. This year's ethics session, following that initial session suggested some solutions to the problem, but it still leaves much to be desired. The ACNP, I think, has to play a central role. In our field, and I don't have to tell you, we work with industry to develop drugs. This is what we do.

DK: However, you must have been very fortunate in the amount of traveling you've been able to do. Tell me about some of those places you've been to.

IG: Well, I've been lucky in taking what I learned from meetings like ACNP around the world. In the mid 1980s, I got a Fulbright grant to teach in Italy and Japan. I told you in the 1970s I was heavily involved with family therapy and with medication, so I spent a half a year in Verona at the School of Medicine, teaching family therapy and psychopharmacology. In the other half of the year I went to Japan working on a study that I started here in which we followed up patients who had mood disorder to see what happened after the hospital. The study was really a labor of love. What I found was that cultural differences had little effect on outcome among Japan, Italy and the United States. The main finding was those patients who had a good outcome, had two interventions in the hospital, which differentiated them from those who didn't do well. You had to not only prescribe medicine but you had to take it in adequate dosage. The second issue was that you had to have had a significant other or family who received psychoeducation about the illness. Those two variables, adequate medication and family intervention, were highly correlated with outcome. If you didn't have these two, you went right down the tubes. You were readmitted two or three months later or relapsed or something like that.

DK: Did the family had to be educated?

IG: Yes, we had to do psychoeducation. You had to do psychoeducation to educate them; what's the nature of the illness; what's the nature of the treatment; and what can you expect. And here are some coping strategies. So, we built a whole module. Where the programs were good, the patients did much better. Then, again, short hospital stays are still a

huge problem. What's happening now in hospitals is that patients come in, they all get a diagnosis of psychosis NOS or mood disorder NOS, and everybody gets a "shotgun blast" of medication. There's very little contact with the family, so it's another study that remains to be done.

DK: Do you want to do it?

IG: I ought to do it.

DK: What might you be doing in the near future?

IG: Really, my primary efforts continue to be working with new drugs as they come out. I really enjoy trying to find out more about how they work in clinical practice. A lot of the small studies that I've done with these new antipsychotics speak to what works and what doesn't. I've done two studies of concomitant medications for schizophrenia. Essentially, concomitant medications don't do anything in schizophrenia, including mood stabilizers and antidepressants. ACNP taught me to ask the questions, what works, what doesn't work. Those are questions that are not commonly being asked in clinical practice. So, that's kind of thing that I have been doing and I intend to continue to do work with the new drugs. So if you can find new medications with different mechanism; perhaps, serendipitously, that would be a great joy to me. The other area that I've really worked hard on is this psychopharmacology curriculum, which has taken up a lot of my time. I've shepherded it. I have a large group of people working on it and getting it out there, that is getting it marketed, and getting it used. Showing people how to use it has been a real labor of love. It's been helpful for the field. The ultimate aim is to try to improve the quality of pharmacology practice. "Quality indicators" is where I'm headed, i.e. trying to improve the average clinician's practice. It's no longer the question of, should we give medicine, but but can you give it competently as well as keep up with the advances in the field. A meeting like this has always been the place where one could keep up, so that's important.

DK: From your point of view, what about the difficulty in time constraints? There's only a limited amount of time you can spend with patients.

IG: Well, from my perspective, I've emphasized not only talking to patients, but as importantly talking also to their significant others. I almost never see a patient who has Axis I disorder without a significant other, so you need adequate time in the office. This tactic is not popular with insurers. To actually do the job of working up a patient, find out what's wrong and what you need to do, takes time. So, that's a very important and unresolved issue.

DK: I was just wondering whether that restriction on practice has constricted the ability to do research.

IG: Absolutely. Clinicians aren't going to sit there and spend precious time to use rating scales to follow progress. And, I should say too, here in the ACNP, there's been a shift away from clinical psychopharmacology to a greater focus on neuroscience. That's happened over the years, thirty or forty years. It's an important trend, whether it's ultimately going to pay off or not remains to be seen. Finally, on a different topic, I should mention that eight years ago I started an educational session at the annual meeting focused on teaching psychopharmacology. The impetus was my realization that ACNP had a dual mission the first being research, while the second was education. Education Day had focused on a particular topic, like "genetics and psychopharmacology," but little attention was being paid to pedagogic issues. To fill this void, we developed eight sessions. The topics were: (1) The Field; (2) The Curriculum; (3) The Focus on Improving Practice by Improving Teaching; (4) The View of the Teachers; (5) The Neglected Constituencies: Can Teaching About Psychopharmacology Change Attitudes & Practices?; (6) Teaching Cutting-Edge Psychopharmacology: What Works and What Doesn't; (7) An Epiphany for Psychopharmacology Education for Residents and Practitioners: A Demonstration; and (8) Teaching Psychopharmacology: Successes and Failures in Determining Whether Anyone Learned Anything, or Did the Message Get Across? Attendance has averaged between 75 and 100 ACNP teachers and travel awardees.

DK: OK. Thank you very much. We'll see you around.

IG: Thank you.

GEORGE R. HENINGER

**Interviewed by Thomas A. Ban
San Juan, Puerto Rico, December 2003**

TB: This will be an interview with Dr. George Heninger* for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the college in San Juan. It is December 7, 2003. I am Thomas Ban. Let's start from the very beginning. Would you tell us when and where you were born, brought up and something about your education?

GH: Sure. One of the psychological threads through this was that both my mother and father were strong Mormons when they got married. My father had been raised as a farmer, but sort of discovered education; so he was going to school intermittently as he was farming. He met my Mother and they got married. After he finished college, my father went to the University of Chicago for medical school. So my brother and sister were born in between there. I was the third child, born in California during internship in Los Angeles County Hospital. There was a polio epidemic at the time.

TB: What year?

GH: 1934.

TB: '34.

GH: They eventually went to Phoenix for a little bit of private practice, then back to Salt Lake City for a couple of years, where my younger brother was born, and ultimately we moved to Provo, Utah, where he became superintendent of a mental hospital, a position he held for the rest of his life. And that's how I essentially was raised from the age of 5 until I went off to college. The reason for choosing psychopharmacology came from maybe two or three dimensions. My father studied with Ralph Gerard in Chicago, but had to feed his family, so he gave up research to practice but he was always going on about how important research was. So that was always in my head. As a senior in high school I had a project on antibiotics. They had just invented penicillin and streptomycin. So it was a miracle story of drug discovery and application. It saved a huge number of lives.

TB: This would be in the early 1950s.

GH: Yes, that would be 1953. The idea that you could do research on the way chemicals altered body function was a major issue. I went to the University of Utah in 1953. I was going to be a PhD biochemist, and I came down with rheumatoid arthritis as a freshman, which threw me off

* George R. Heninger was born in Los Angeles, California in 1934.

the schedule. I couldn't make all the classes. So, instead, I just went to three years of college and then right into medical school. And they let us do that in those days.

TB: So, three years of college and then medical school.

GH: In medical school, I started off in the laboratory of Dixon Woodbury. So the Goodman of Goodman and Gilman was there, and Dixon Woodbury was a major player. And we studied the effects of carbonic ion hydrases in anticonvulsants. That was my first study. And I worked in his lab all three summers that I was there, which got me started. I did well in medical school, so I was able to get the best internship from our class, which meant you could either go to Hopkins or to Boston City Hospital. I picked Boston City Hospital because at the time I had just started reading a few papers, maybe some of yours, in psychopharmacology. So it kind of came out of anticonvulsants that I went into psychopharmacology. And I choose Mass Mental because of Al DiMascio and Gerry Klerman. So I specifically targeted Mass Mental after my internship for training. And as a matter of fact, I worked all three years with Al DiMascio and Gerry Klerman on their clinical neuropsychopharmacology research unit. I also did my clinical training; I was a chief resident there. And that launched me on a career of clinical neuropharmacology. I had two years in the government because of the Vietnam War and public health service, and I was at St. Elizabeths with Fritz Freyhan for one year, and then I was at the Clearing House for Mental Health Information Center for a year.

TB: You worked with many distinguished people in the field.

GH: Well, the one I miss the most is Al DiMascio. He was a unique character. I've never met anybody like him before or since; very gregarious, robust, Italian, overweight, unstoppable. He didn't have a PhD. when I started working with him. He got that a little bit later. But he had the idea that you could use drugs in healthy humans, look at their behavioral profile, and then you could predict what those drugs would do in illness. We were using, and that was 1960, some of the first neuroleptics and antidepressants in the country. Mass Mental Health Center where I trained was very, very analytic. Gerry Klerman sort of straddled the boundary. Al didn't get caught up in the politics or anything. He just went ahead with his research and submitted applications for grants. I couldn't think of a better person for a young investigator to work with because he was so giving. I attended the ACNP meeting in 1961 with Al. I think it was about the second meeting. He always took me there. And he would include you in his research. I did the legwork in Gerry Klerman's and Al's study in which they gave some drugs to healthy subjects. In one study by accident they got a bunch of athletes from Tufts, and a bunch of bookworms

from Harvard, and they found different responses. So they thought that personality affects response to drugs. What they found was that athletes that were mesomorphs and very active would not enjoy sedative-type side effects, and that the leptosomatic, skinny, bookworms, wouldn't mind being sedated. It kind of came out that way. But we gave 400 mg of chlorpromazine orally to young men, and they went to sleep on the floor from it. It just knocked them right out. The idea of another study we did was that desipramine was quicker acting than imipramine because it was de-methylated. And we compared the pharmacological profile of the drugs in normals, and what showed up, was, the anticholinergic effects of imipramine. Dry mouth and all of the anticholinergic effects were prominent with imipramine. So that gave me a good start. Mass Mental at that time was the premier residency training in the country, academically. There's no question about it. There, ahead of me was Eric Kandel. The year behind me was Herb Meltzer. In my year, it was Dick Shader. So it was just the place to be. Dick Shader ran the first comparison between drugs and psychoanalytic psychotherapy at Mass Mental at that time. Joe Schildkraut was there. So I worked with Joe Schildkraut for a whole year. It was a real good starting point. The institution itself did not support research much. You had to do it yourself. I wanted to work with these guys. Greenblatt was there. So you'd just go over there and work. The training program itself was analytic totally. It didn't have any research component to it. Anyway, that set me up with better credentials so I got a good spot at St. Elizabeths with Freyhan. That was a little harder. Freyhan had, in my opinion, more fixed ideas. It was more of a European, a little bit more authoritarian than I was used to. He would sort of tell you what to do. He'd have categories of paranoia that were very important; to me, all the paranoia was kind of the same. For me it wasn't important one kind of paranoia, but for him it was. I got started with Louise Speck there who was doing research with cerebral evoked potentials. The first person ever to do that kind of research was Charlie Shagass, a member of the college. Louise Speck had the first computer used in electrophysiologic work. Anyway, we did evoked potentials in schizophrenics with light flashes.

TB: So, this research was done at St. Elizabeths?

GH: At St. Elizabeths.

TB: So, you did research with cerebral evoked potentials with Louis Speck while you were working with Fritz Freyhan at St. Elizabeths? Did you work also with Joel Elkes while there?

GH: No. He was sort of the mentor of the whole thing.

TB: I see.

GH: Bunney and Davis and Shildkraut get credit for the monoamine theory of depression, but really it came from a guy named, I think, Dale Friend, who worked at Peter Bent Brigham Hospital. It was just across the street. He was an endocrinologist, and he gave these guys the idea that depression might be related to low metabolism in the norepinephrine system. They didn't think that up. He thought it up, and that's how the idea of the monoamine hypothesis of depression came.

TB: I see.

GH: So I worked at Mass Mental in 1957. We were doing rating scales on depressed people on the ward, and that was my job. And when Max Hamilton came as a visitor we met him and asked him about his scale. It was amazing that Max made this scale up out of his back pocket just by talking to patients; he just wrote down stuff. And to this day, it is his scale that huge pharmaceutical companies use. Max just made it up in a coal town interviewing depressed people in England, and it stuck.

TB: Did you use the scale extensively at St Elizabeths the time you worked there?

GH: Well, I did it in most of the patients at that point. And, then I went over to work at the National Clearing House for Mental Health Information for a year and ran the Psychopharmacology Abstracts and things like that as a sort of bureaucrat. We also sent out surveys to find out whether people read the Abstracts and things like that. Then I got a job at Yale through Gerry Klerman, who had then moved to Yale; he was staffing a research ward and hired me and Malcolm Bowers to run the research ward. I wrote a grant while I was still at NIH. You can't submit it while there, but you can write it. I wrote it on evoked potentials in schizophrenia; and I got the grant. And because at Yale there were some people who had a bigger computer by now, I got a tape recorder that I could use for the recording the evoked potentials and then took it to the computer and processed it. To give history a flavor of the way things were at that time, grants were much easier to get. My old mentor, Eugene Bliss, from Utah, was on the committee that reviewed my application, and he said to me, well, I didn't think it was a very good idea, but you're a smart kid so we thought we'd give you the money. And it wasn't a good idea, because I was going to do somatosensory, visual and auditory evoked potentials in patients with somatosensory, visual and auditory hallucinations. Well, you don't find people with somatosensory hallucinations. They don't exist, you know. And, few visual hallucinations are seen in schizophrenia; mostly all hallucinations are auditory. So, what actually happened is, I started doing those, and I actually ran my own lab at that point.

One thing that had happened down at NIH, Louise Speck had gotten into spectral analysis of EEG, and I had some data from that which I wrote up and tried to publish. In the meantime, I had set up my own system to acquire EEG and do spectral analysis. And the results that I had from her didn't fit with what I was seeing. It sort of brought home the point that you've got to do it yourself if you really want to trust the data. You know, you've got to know where it's coming from; you don't see anything in the spectral analysis you can't see with your naked eye. All what spectral analysis does, it magnifies. We did evoked potentials in schizophrenics when they were sick and then gave them chlorpromazine and they got a lot better. Nothing changed on the evoked potential. It stayed the same. The thing that I stumbled on with manics was that they didn't respond well to chlorpromazine. It was just about the time that lithium became available.

Lithium was first given at NIH in 1961. There were two wards at NIH: the John Davis ward and the Fred Goodwin ward. They were two competing wards. And both Davis and Goodwin gave lithium to their patients and both reported to Kety at the same time their findings. It was funny that the two guys were so competitive, that they reported it secretly. They wouldn't tell each other what had happened.

This was the year before I moved to Yale and since chlorpromazine didn't work as well I decided to use lithium in our subjects. So, this was the first time that lithium was used in Connecticut. And it made a profound change in the evoked response. So, I spent the next four or five years showing that the evoked response to lithium on the EEG would give you a quantified measure of the effect of the drug on the physiology of the brain.

TB: So, you studied evoked potentials with lithium?

GH: I only published a little bit of that data because I felt that my data were not perfect. We had patients talking to you with Δ -waves in their EEG. I mean, they would be in Stage III and IV sleep, but they would be sitting there talking to you, because the lithium would give you those huge slow waves. One of the unusual things lithium produces is an increase in the early somatosensory response. I thought, well, I could investigate that in animals. So I set up another lab for research with animals.

TB: Did you have any training for working with animals?

GH: No. I had used people only before, but I was in a very rich environment. The Connecticut Mental Health Center just opened up and there was a lot of money infused. Their research ward was free care, so that was a big thing. And then several labs were opening up. To this day it is an extremely rich training environment for young investigators. John Flynn

was the director at that time, and he had a lot of animal experience. Mike Sheard was there, and he had also animal experience. So we collaborated, and ended up putting electrodes in the brains of rats, cats, and monkeys. I did work for several years with implanted electrodes to see if we could get an idea of what lithium is doing by looking at evoked potentials, and levels of lithium. Probably, in terms of my career, it was when I had the most energy; I was young and ambitious. It ended up for me not being that productive because I couldn't get down to the specificity I would have liked to. I needed biochemical with the physiologic measures. I got very disenchanted with evoked potentials, because we stuck in electrodes on the cortex, and if you moved the electrode 1/8th of a millimeter, the whole potential would invert or get bigger or smaller and all the huge amount of information was lost. I even got to the point of trying to record single units in monkeys, but that was technically so difficult that I gave it up. And a new approach was sort of emerging at the time. During this time, maybe for 10 years, I was unit chief on the research ward. At a certain point in time I switched from physiology to pharmacology in my research.

The strength at Yale was Nicholas Giarman and Danny Friedman, who in 1957 set up the biologic sciences training program. That program is still present. George Aghajanian was trained under that program. Floyd Bloom was there under that program. And that program was classic neuropharmacology. All the principles of pharmacology applied to the brain, and it was just straightforward and extremely productive.

TB: After you switched from physiology to pharmacology what did you do?

GH: We started to have ideas about specific compounds targeting specific receptors. That was when we wrote the paper *Monoamine Receptor Sensitivity in Antidepressant Drugs* and things like that. And, then, it happened to be I was lucky enough to have a number of young very energetic people come in, Dennis Charney being one. And we did a whole series of studies using the best drugs we could obtain to probe the different transmitter systems, e.g., GABA, the monoamines, etc. And that was very productive. We also studied the effects of tryptophan depletion.

TB: I suppose we are now in the 1970s?

GH: We've gotten up into the late 1970s, and early '80s. I must say that was an evolution for me to get into classical neuropharmacology. By that time I had become Director of the research facilities, both the lab and the ward. And, then, the notion of receptor subtypes started to come up; that brought us to the molecular level. Then, we went out and recruited John Tallman and Dorothy Gallagher from NIH to strengthen our molecular

investigations. A study was designed to look at receptor subtypes in the benzodiazepine system and develop drugs for that.

I was, at Yale for 13 years Chief of the Research Ward, and then I was another 13 years Director of the Research Facilities. There was a lot of politics of trying to keep your funding up and things like that.

In 1960 when I graduated, I bought a few books on psychopharmacology; there might have been four or eight books on psychopharmacology altogether. That's all there were. You didn't have to worry about the size of the literature. It was that big. You could hold it. There were some far-flung, some futuristic ideas of being able to specifically alter mental function, almost like smart bombs do in war, to target exactly.

TB: It was thought that we will have drugs that work as keys in their locks.

GH: Yes, exactly, and with real specificity. That dream is still present as the central goal of neuropsychopharmacology, and to some degree we have moved in that direction with the SSRIs. They don't have the side effects that tricyclic antidepressants do, and we can get about the same efficacy. Since we don't know the pathophysiologic pathways in mental illness, we don't target exactly the abnormality, as in diabetes or some other diseases. It was for getting there that we started at Yale research with Tallman, who brought in Nestler and Duman, at the molecular level. It was a movement toward a more fundamental understanding of the processes involved in psychiatric disease. For many years we haven't made a lot of progress but in recent years we've made progress on learning about cell loss and things like that in both schizophrenia and depression. It's still not clear why that's happening, why stress produce neuronal loss. Then, in 1993, I turned over the leadership to Eric Nestler, and Nestler was there for awhile and then in the last four years or so, Ron Duman has been the Director. I've moved into having more teaching activities.

TB: Now, let me ask you: what would you consider your most important contribution?

GH: It would take somebody independent to judge this. I think my greatest contribution is in training people. We have 6 people that are chairmen of departments of psychiatry that trained on my unit.

TB: Who are they?

GH: Well, Dave Kupfer is the first.

TB: Who are the others?

GH: Tom Uhde, Eric Nestler, Chris McDougel, Pedro Delgado, Steve Bunney, Mark Gold, Larry Price, Wayne Goodman, John Krystal and Dennis Charney.

TB: Would it be correct to say that you feel, that, your most important contribution was training these people?

GH: My major contribution is sort of like of a housewife. I defended the research unit against encroachments from the state, because they were going to shut it down. I recruited a pretty good team of people. And then we sort of set up a milieu, an environment, in which they did very well. So, training is the best thing I've done. I would like to say I'd discovered something fundamental...

TB: Did you have a clinical practice?

GH: In residency I was a Chief Resident on a regular unit, and I did a good job. And I had 6 trainees under me, and we did a good job there. With Dr. Freyhan I ran a clinical unit. And when I came to Yale, for 13 years I ran the research unit. We always had three residents on that unit every year. That's where a lot of the trainees came from. Ken Kendler trained there. So there were some big names that came through there. And we took care of the patients on the unit. I had a little private practice too. I had some patients; not a lot. I spent 10 to 20 hours with patients weekly.

TB: So you combined teaching with administration, research and clinical work. You have also published quite a few papers.

GH: Yes. There's a few more in the box that never got out.

TB: What was your first publication?

GH: The first one was probably the one we did with Louise Speck on cerebral evoked potentials in schizophrenia.

TB: When was it published?

GH: That would be in 1964, or '66. Let me correct: the first one was probably not that but the one with Al DiMascio in which we compared in normal subjects imipramine, desipramine and an imipramine-desipramine combination.

TB: What did you find?

GH: Well, the biggest finding was sedation with imipramine.

TB: And as you said early the desipramine subjects did not have anticholinergic side effects.

GH: Well, with imipramine, it was just sedation in normals. And, of course, their tapping speed would slow down.

TB: Did you measure also perceptual changes?

GH: We measured psychomotor changes but did not use perceptual tests.

TB: Didn't you carry out also another study in normal subjects?

GH: Well, I did another one with DiMascio. We studied relationship between personality and drug effects. We gave trifluoperazine and chlorpromazine if I remember that right and some of the leptosome people developed EPS. I remember we had dystonia in one kid; he was a skinny kid. It sort of interested me, because I haven't seen as many fat people get dystonia as I have skinny people.

- TB: Was the dosage in the study adjusted to weight?
- GH: No., it was just a straight out dose. We just gave them so many milligrams.
- TB: So you co-authored your first a paper with Al DiMascio?
- GH: Well, Gerry Klerman was also coauthor. The effect of personality on response to drugs was a pretty big study; it was hard for me without any prior training to do the data analysis and the statistics. So that was like all new to me and Al was the only one I could talk to.
- GH: Then, you also co-authored a paper as you mentioned with Louise Speck.
- GH: We did that one paper with Louise Speck.
- TB: One paper?
- GH: One, and then another one that never got accepted. I eventually found out that the data were wrong. The numbers we had did not jive with what everybody else had seen in schizophrenia. .
- TB: Didn't you publish your findings with lithium?
- GH: Well, I published some findings as a single author. I did the whole thing.
- TB: This was the evoked potential study with lithium. Could you tell us more about that study?
- GH: Well, you give an electric-shock on the wrist and that goes up and gives you an evoked potential. And in about 20 milliseconds there's an early negative wave that is followed at about 25 milliseconds by a positive wave. If you give a barbiturate, the response does not change. At the time, I thought that was pretty profound. Now I know that it's not as profound. The EEG slowing even if not as specific, it is more sensitive. We did studies where we gave people placebo, then lithium, then placebo again, and then we administered psychometric tests. We were able to correlate the EEG changes with the psychometric changes. What it boiled down to was that lithium produced slowing of psychomotor performance. But if you look at depression, that does it too; depression will slow you down. You don't perform as well. And we were able to dissect out the lithium effect from the depression effect. Another thing we found out that rodents, don't metabolize lithium the way humans do. There are big, huge differences. So a lot of the work we did with lithium on rodents is un-interpretable. Cats are a little bit closer to human in metabolizing lithium than rats, and monkeys are even closer than cats. Still, there were times when we had very high lithium levels in monkeys and no evoked response changes. It had to do something with water balance, because when we hydrated the animal, then the evoked response would get bigger. I gave up trying to figure it out. That was the time I shifted from physiology to classical pharmacology. It was hard to give up a career, sort of, in evoked potentials. Later on it was not hard to switch from neuroparmacology to molecular biology; they're the same. Another point is that our residents don't use lithium very much anymore.

TB: What are they using instead?

GH: Valproate. Valproate has been advertised and proposed by lots of people. All the speakers come around and talk about valproate and they don't talk about lithium. I think there's a spectrum of illnesses within the bipolar group of diseases and lithium has a proven track record in some of those illnesses. It's true that it has also a lot of bad side effects; worse than valproate on average, just taking everything in. I think the problem is that there's times when you need to use lithium, and young people are scared of using it because they've never used it before. Another problem is that they do not like to monitor the blood levels. So, they would rather not measure blood levels and use valproate. But there are some people that do much better on lithium.

TB: You did quite a bit of research in depression.

GH: Yes. I chose depression because the people get better with treatment. Schizophrenia, in the classic sense is a neurodegenerative disease. It's like Alzheimer's. I mean, nobody gets better from Alzheimer's. They stay that way. If you don't have the neurons, treatment is not going to work. But people can get 90% better from depression. I don't think they get 100% better, but 90% is pretty good. So that meant that there was a process, a biologic, metabolic process going on that was present before and not present after treatment. I had a patient who cycled every other day; one day he was depressed and the next day he was totally normal, or a little bit hypomanic. He would do that for a month. When he was depressed he had all the classic melancholic signs, and then within 24 hours he would be like normal. That was written up in a paper that was published with Kupfer. It was the first paper that Kupfer published from our unit.

TB: What are your current activities?

GH: I have a training grant. I've had training grants all the way. The one I currently have is for putting the neurobiology of psychiatric disease on the Internet in such a way that it's usable by medical students and residents. We're designing a participatory program that gives them a score from which we and also they know how well they do.

TB: What about research?

GH: I've shut my lab but we have just looked at cytokine levels in the CSF in OCD.

TB: Have you been involved with any research with drugs lately?

GH: The last one we did was a study of ketamine, an NMDA blocker in depression. We got good results in a small sample, but nobody has replicated it.

TB: When was it published?

GH: Two years ago. Bob Berman who did it moved to Pfizer. We keep losing all our people.

- TB: Is there anything else relevant to research in psychopharmacology you would like to tell us?
- GH: I guess I would say, to have on the tape, the importance of participation of young investigators in the ACNP; to get the young people involved. They had been major changes taking place in research over the years. I got involved in research in 1961 and I remember that I had to submit my research proposal to Daniel Funkenstein at Harvard. To do our study, I had to take a piece of paper and get him to approve. It really upset me that some other guy would have to approve our work, as though we were going to try to hurt people or something. Now, that has become an industry at this point. People now are going into ethics as a specialty. And also the FDA regulations have changed. We used to be able to get hold of drugs from the companies and give them to subjects in our research. Now, the independent investigator is caught between a huge pharmaceutical company that won't give you neither any information, nor access to drugs, and the FDA who won't let you do anything until you get all the data on the toxicity of a new compound. Toxicity studies for a drug costs over a million dollars. So the use of novel compounds in clinical psychopharmacology by independent investigation has almost stopped. It has just stopped. Because of those two factors some pharmaceutical companies that were liberal initially became so conservative that they wouldn't give us access to any compounds. So some ideas sitting around are at least 15 years; 5HT_{1A} receptor agonists have still not been used in depressed people.
- TB: Let me switch and ask you about your activities in ACNP. Do you remember the first meeting you attended?
- GH: I came to the first meeting in 1961, with AI, as I told you and then I came in 1964 or '65 again and intermittently thereafter.
- TB: When did you become a member?
- GH: I became a member in 1980 or something like that.
- TB: Have you served on any of the committees?
- GH: I've been on the Credentials Committee a couple of times. And I'm on the History Committee now; and on the Ethics Committee next year. I think those are the main ones.
- TB: I just have a couple of more questions to ask. Is there anything you would like to see to happen in the field in the future?
- GH: What I would like to see has already happened, and I'm totally amazed. You can go on the net now and get the original publication quicker than you can get it out of your own library. I mean, I can get an article from the archives of neuropsychopharmacology quicker on my desk than I can go downstairs and go through the journal and pull it out. And it can be filed

on your computer and accessed later. So I think the information transfer is a miracle. It has really changed the world. It's instantaneous. The journals are a little slow. Their archives are slow. But, you know some of the neuropharmacology and biological psychiatry journals are speeding up their review process. So, that's good. In general the papers could be shorter but the information in papers larger, so that you could read the paper and get to the point sooner. It would also be good if the raw data, the actual numbers that form the basis of the paper would be available for your computer. So you would upload that and you could do your own analysis on the information. That step is not quite yet taken.

TB: Anything else?

GH: Oh, well, yes. But they're all fanciful.

TB: Tell us.

GH: I would like to see an organization that would be above the FDA that would have health as its main concern, not just the regulatory issues, and that that organization would be able to order the FDA to give individual investigators access to proprietary information that is on file with the pharmaceutical companies. So, if I want to get an individual IND for any drug I should be able to get all the information on it. You know, there are lots of things that just shut the individual investigator out, and I think that has really injured the rate of progress in research. I would like to see also an organization that forces all clinical studies to be public domain information. The pharmaceutical companies conduct extremely expensive and sometime dangerous studies, and none of that data is ever available to the public, to anybody. It's locked away. And there are children who are getting pharmacologic trials, little kids, and if the drug isn't effective, none of that information is available to any investigator, to anybody else. It's invisible.

TB: These are important issues.

GH: It's essentially an industry that is polluting the environment. And if you do that in a steel mill and you kill people with smoke, it's against the law. Yet, the pharmaceutical lobby will squash any attempt to change the system. So there needs to be a new organization that rewrites the law in order to make all the original information public. The information has already been obtained, it's already there. But you can't see it.

TB: Do you think ACNP should get involved in these issues?

GH: The ACNP has been unable to change this problem. I'd just put a plug in for the ACNP. The ACNP is not as important in some areas as it thinks it is, but it's more important in some other areas than it thinks it is. The Society for Neuroscience is a much bigger organization, and it produces humongous advances. There are 30 to 40,000 people in their meetings

and not just hundreds as we have here. I would think the ACNP could do a little bit better by sort of enlarging itself to a little on the model of neuroscience.

TB: On that note we should conclude this interview with George Heninger. Thank you, George for sharing this information with us.

GH: Thank you.

FRITZ A. HENN

**Interviewed by Andrea Tone
San Juan, Puerto Rico, December 15, 2004**

AT: My name is Dr. Andrea Tone and we're at the 2004 ACNP Annual Meeting in Puerto Rico and, this afternoon, it is my pleasure to be able to talk with Dr. Fritz Henn.* Thank you for agreeing to be interviewed.

FH: Well, thank you for asking me.

AT: Let's start at the beginning. Tell us a little bit about your upbringing, where it took place, how you became interested in science and medicine.

FH: Sure, I was born and raised outside of Philadelphia in an area called Ridley Township and had immigrant parents, who had left Germany in the 1920, went back in the thirties and looked around and said, "Oh, my God", and left again. They were very convinced that education is everything, because following the first, World War, they had to stop school around the eighth or ninth grade and came to the United States, self-educated. My dad, somehow, turned himself into a fairly advanced engineer but felt that we really should study. And, I grew up in a school district that was not academic. It was very, very athletic. We had the best football team in the state of Pennsylvania. We weren't beaten the three years I played from a sophomore to senior.

AT: My, you played!

FH: Oh, I played. The coach was a mad man. We had August camps in the mountains and it was an enormous bonding thing, because you hated it when it happened, but after the season was over, the people on that team were very close to one another. I never thought much about what I would do and I was not, particularly, interested in medicine. I was interested in science, mostly in chemistry. I realized I was not a really great football player, but I came from a really great team and our kids were getting recruited at really good schools. So, I applied to schools such as Swarthmore, Wesleyan and Amherst, Cal Tech and got a series of interviews and ended up going to Wesleyan, and that really changed me, because Wesleyan was intellectually, incredibly active, very liberal school, at that time. It still is, I think.

AT: What time was this?

FH: I went there in the fall of 1959 and was very interested in Chemistry but I couldn't make up my mind between Chemistry and Philosophy. I even took a philosophy course with Hannah Arendt.

AT: Wow!.

* Fritz A. Henn was born in Ridley Township, Pennsylvania in 1941.

FH: It was really interesting. I wrote a paper in which I claimed that Sartre's major work was a satire for Hanna Arendt. I claimed that he was trying to pretend to be a Heidegger, but the whole thing was a bit of a hoax. And, she called me and told me I was either, going to fail or get an A, and she was going to wait awhile to decide. I got an A. It was an incredible experience, because, at that time, Wesleyan was a very small boys' school and we had these phenomenal professors like Hanna Arendt, Norman O. Brown, a well known psychoanalytic historian. We had classes of 6, 8, 10 people. And, that, really, was an incredible education and I in the end decided, I was really interested in Chemistry and we, also, had a very good chemistry department and I thought I would go to go to graduate school in chemistry. In my senior year the Watson and Crick model made an impression on me and I decided, maybe, biology was the thing to do, but I'd never taken a biology course. I'd only taken physics and chemistry.

AT: Tell us about the Watson and Crick model.

FH: Well, this was the structure of DNA and, of course, it looked like it was going to open up the whole area of biochemistry and understanding how genetics might, conceivably, work. And, so, I decided I would study biochemistry. The problem was that I'd never had a biology course, so I applied to Hopkins and Harvard for graduate school, figuring that I would just take one biology course in the last semester, in my senior year, and that would be enough. And, surprisingly, I got into Johns Hopkins, which, at that point, had extraordinary biochemistry department with Albert Lehninger and Dan Nathan, who, subsequently, won the Nobel Prize. They were our teachers and they only took six students a year; only three were undergraduates. And, my wife was one of those six. She went to college at Mount Holyoke and we met at Hopkins. Hopkins was a marvellous scientific education, but what really influenced me was, and she might kill me for telling this story, it was a really tragic educational misadventure for her. She was the best of the students, of the six of us. And, she wrote a thesis, very quickly, that disproved a particular mechanism that was in vogue in biochemistry and it was her advisor's mechanism. She turned in the thesis and her advisor who had treated her very peculiarly, locked her in the lab without a technician and left Schopenhauer passages underlined in the anti-feminist places. He refused to accept her thesis. Then Lehninger, the Department Chair called her in. I don't know if I should ever tell this in public but it is illustrative of the problems women had in science in the 1950s and early '60s. He told her that he couldn't accept her thesis, because it would ruin her advisor; he couldn't deal with being wrong. And after all, he said, he was a woman, she would have

kids anyway, and I was going to be a successful academic. He also said that if she told anyone about this including me, I would never get a job in American biochemistry. He then confiscated her notebooks with the data. That was in the mid-1960s. And, of course, she told me.

We transferred to the University of Virginia, where my advisor had just taken the Chair, and, I finished my PhD thesis, which showed that black lipid membranes were bilayers and could serve as a cell membrane model. Suella did a complete new thesis with Gary Ackers, who became the professor of Biochemistry at Washington University. Lehninger didn't say anything, even though he had refused her the right to work with an ex-Hopkins faculty, which Gary was. At that point, I decided I would go to medical school just to be sure I could get a job. I applied to Virginia and Vernon Mountcastle, a very famous physiologist at Hopkins, called me up and said, "You know, you're crazy. You should come back to Hopkins. You're good and Hopkins is very good and that is where you should go to medical school". And, I said, "I wouldn't go to medical school, there". I didn't tell him why "I wouldn't go there under any circumstances". So, I did medical school in Virginia in three years and took my fourth year as a post-doc. I was interested in learning and memory and I thought, well, there are two places that look really interesting. One of them was in Paris with Tauc; he had just done a paper on heterosynaptic facilitation, which looked like it might be basis for thinking about memory. And, the other guy was Holger Hyden in Sweden, who had these worms that he trained and, then, he took their RNA, and injected it into rats. And that seemed unbelievable, so, I thought, well, I'd better go to Sweden and see what's going on.

So, I got one of the first, maybe the first, Life Insurance Medical Research Fund Fellowships, created by the life insurance companies and the pharmaceutical industry to support Combined MD, PhD training programs. So, I went to Sweden after the birth of our first child and I took the entire Fellowship and invested it in a stock, which doubled and, then, went to zero. So, we were stuck in Sweden with, essentially, no money, which was not good for Suella, who had finished her PhD at this point in time and had been on the Virginia faculty. And, winter in Sweden was very gray, but we got by because somehow, Suella made friends with butchers and bakers and we got through. I had paid the rent a year in advance, so we had that. And, I was working with Andreas Hamberger trying to separate neurons and glia. In pharmacology, Arvid Carlsson, and Annika Dahlström were right above my office, but I hardly ever talked to Arvid. I didn't know him at that time. I was interested in biophysics and I was interested in transmitters, at the time. I did know Annika a bit better,

because we shared tennis dates, but I was aware of what was happening with the amines. That's the point in which the catecholamines were just being mapped. Annika and Kjell Fuxe had just published their paper so it was an exciting time. And, in Hopkins, at that time, and, in NIH, Julius Axelrod's group, especially, Leslie Iversen and Sol Snyder were making a point that you could identify synapses by monoamine uptake, norepinephrine uptake or serotonin uptake. And we were isolating neurons and glia. We developed ways of pushing the neurons and glia apart to isolate cells. When we did this, we saw that the astrocytes had glutamate and GABA uptake systems. We felt this was important and published it in *PNAS*. It took over a year to get it published because no one believed us and the reviewers, I later learned, Leslie Iversen and Sol Snyder, were against this idea initially, because it was against the dogma then prevalent. The reason I'm spending some time on this, because the most exciting developments at this (ACNP) meeting in 2004 was Sol Snyder's symposium on *How Glutaminergic Synapses May Really Be Controlled*. The gist of it is, probably through glutamate uptake systems and astrocytes, so Sol has come around.

AT: It's taken awhile.

FH: Thirty-five years, which he announced. He admitted it in the symposium and that was really nice for me, because I had a terrible time in the '70s getting this stuff published; although, some of it appeared in *Nature*. I mean, it got published, but it was very, very fraught with controversy. And, about that time I was always convinced that this would be a way to control synapses. However I needed to get my specialty training. And, so, I took a resident position in psychiatry at Washington University at the time when the Feighner criteria were established. So, the group of residents, right before me, included John Feighner, and we had all sat around a table and simply made these criteria up from the old Kraepelin stuff. The idea was to be able to communicate with each other, and could form homogenous groups. We never felt that would really be the diagnostic classifications, but, as you know, that led to the RDC and the DSM-III, that became an industry. So, I had gotten interested a little bit in diagnosis. Then, one of my teachers at Washington University, George Winokur, went to Iowa as the chair. When I finished I applied for jobs at Harvard and Wash U and got them both. Then, George said, "Why don't you come to Iowa"? And, I said, "Well, George, I don't know". And, he said, "We'll meet at the APA in Detroit and we'll go out to lunch and I'll tell you why you should go". So, I went up there and George took me to a hot dog stand. If you knew George Winokur, this was perfectly in character. He bought me a hot dog and explained to me why I should

join his faculty, which I did. My wife agreed. The point was we had two children at the time I and we decided it might be enormous fun to buy a real working farm, which I did. So, I bought a farm and it was in the middle of nowhere. George thought I was completely nuts but we went to Iowa. The farm was rather rundown and we decided we'd raise cattle, so I bought cattle and I started to work in Iowa. One of the first people I met there was a woman, who had just joined the staff, Nancy Andreason. She had just finished her thesis on John Dunn and I remember Nancy asking me what an action potential was. So Nancy and I talked about neurobiology and, then, she, subsequently, shattered my research career with her knowledge of neurobiology.

AT: I interviewed her last year. I hate to derail you while you're on a roll, but I'm curious why you chose psychiatry and how it was being taught at the time.

FH: Well, that's another very interesting story. At Virginia, when I did my psychiatry rotation, I thought psychiatrists were all a little crazy. It was a psychoanalytically based department. I was terribly interested, as I told you, in memory and, so, I thought I would rather do either Neurology or Neurosurgery. I was really most interested in Neurosurgery, but I figured I'd be too old with seven years of a neurosurgery residency, so, I decided I'd probably do Neurology. So, at the end of my third year in medical school I took an internship position in Neurology for three months. I was not even graduated from medical school, but they let me do that. I had, also, been involved at Virginia with a little bit of work in organizing a student body and in the Mulholland Society that was involved in trying to make medicine to relate to the needs of the disadvantaged parts of society, to get it out into the Appalachia, for example, and do that kind of thing.

AT: Could you say something about your internship in Neurology and how you got into Psychiatry?

FH: At rounds in Neurology, we would argue like hell about where the lesion was and, then, we couldn't do anything. So, I thought, my God, I'm not going to spend my life doing that, because we had neither imaging nor effective treatments at the time. I thought that neurology intellectually, was wonderfully interesting, but you couldn't do anything. I remember seeing patients die with strokes and go very downhill in some of these diseases such as ALS, for example. I figured, gosh, I really don't want to do that. And I remembered that at medical school I had the most fun with a manic patient. I thought, maybe, this would be something to do; psychiatry is still the brain and these people are at least interesting. You can talk to them and they're great fun and, maybe, I should do this

even if all the psychiatrists are nuts. I had also been reading some of the things that Seymour Kety had done, so, I applied to Harvard and went up to see Seymour. He knew some of the papers that I had written on membranes. They were rather well received at that time. He said, "Yes, you've got to come into psychiatry. Go, interview at the Mass Mental Health Center," that I did and I went through the wards where they were still hardly treating people. They were still treating them with analysis; although, the psychotropic drugs were there, but they weren't using them very much. I was a little appalled at the level of untreated illness that I saw there. Then, I went into my interview with the Director and told him that I didn't like that and they really should treat more aggressively. But, he wanted to talk about my father and do a sort of psychoanalytical interview, so, finally I told him that, you know, we differ so much about how we think about the brain, that there was no point in me applying there. I went back to Seymour and said, "I'm not doing this". And, Seymour said, "You've just got to do this; you've got to just cool it". And, I would have been in a pretty good group of people at that time, I think. Eric Kandel had been a resident there; Judy Rappaport was a resident, but I refused. I said, "They're all crazy". And, so, I went back to Virginia and remembering Seymour's advice, "You should look at Washington University. That's one place that might be different," I went out and saw Eli Robbins and we really hit it off. I said, "Eli, I really need a lab. If I come out here, I can't just do clinical work. I want a lab, as well". And, he said, "If you're good at clinical work, you can get a lab". And, he did keep his word and the first paper I ever published in *Nature* was actually done when I should have been doing child psychiatry. I went to him, after two or three weeks, and I said, "Eli, these families I work with are so screwed up that whatever I do with this kid isn't going to change anything and there's no way I can deal with the families. I can do all this stuff, I mean, if you give me an exam, I'll tell you what the answers are, but I'm not going to learn anything more. Why don't you just let me go in the lab"? And, he said, "Alright, go in the lab". So I did and we, pretty conclusively, proved, using culture systems that high affinity glutamate transporters were really on astrocytes and that paper was in *Nature*. And, then, I went on to Iowa and so it was really Eli, who got me into psychiatry. He convinced me that it was also another way of looking at the brain than psychoanalysts do, that we could do empirical studies and that is what we needed in psychiatry exactly. We needed the marriage of psychiatry and neurobiology. I feel that Eli was the most far reaching person in the field in America in the last hundred years. I think he really was the influence that changed American psychiatry and I think if you really look back, you'll find that almost all of the

modern neuropharmacology that has evolved into the ACNP grew out of what happened when he left Harvard and went to St. Louis and started a very empirical approach.

AT: Which we called the St. Louis School.

FH: When I got to Iowa, we had a very interesting department. The broadest person there was a young man named Mike McCabe. He was killed in a bike accident. And, then, Nancy was there and I was there. Ming Tsuang was there; George was there; Kathy Halmi was there; Rat Crowe and Remy Catorte were there. And, you know, this was a department that only had about nine faculty members; it was really an exceptional group of people, who interacted very well together. We mostly got along and I started lab work, then, George got impatient, because he didn't see that it was going in the direction of psychiatry, so he told me I had to do something psychiatric. So, I kind of gave up the glia work, which was probably a mistake, but I was having trouble getting funding, because I was still fighting with Sol about this. He was much more influential than I was. So, I looked around and, then, I decided I would try to get an animal model of depression and we've worked since the mid-1970s on the learned helplessness model that Marty Seligman developed and we did it in rats. We've refined it a great deal and that shifted my research into something a bit more psychiatric. And, we had this farm all the time.

AT: With cows.

FH: And, I would try to dream up things. We did some very interesting things. I was breeding cattle, so I thought why we couldn't breed chickens with low cholesterol eggs. I spent some money and brought chickens in from the Andes, Aurucana, very beautiful chickens that have green and white and pink eggs and I raised them.

AT: I didn't know that there were chickens that produced green and white and pink eggs.

FH: Oh, well, no one knew that and they thought that my daughter was psychotic in the first grade, because they were talking about brown eggs and white eggs and Sarah said, "No, no, we have pink eggs and green eggs". And, this teacher really called Suella up and said: "I couldn't talk her out of it. I think she's a sick young girl". We brought the teacher over and showed her the eggs. I could change the color by changing the calcium and I used to sell them. They didn't have lower cholesterol. I would bring them into the psychiatry department. One day, George put up a big sign, No Peddling Eggs, which I ignored. He was one of my best customers. And, it was a very interesting adventure and the farming was really very interesting, because we didn't know very much and the neighboring farmers were just extraordinarily helpful. I mean, they really helped us and we

did raise cattle. We ended up with forty cows and getting a cow that's in breech position to give birth at minus 10 in February in Iowa was something that I learned to do. But, I only learned it after losing a cow and the neighbors were there, at two in the morning or at three in the morning, to help you. That was community in the true sense of the word. And, when my daughter was eleven, I think it was, she came to me and said, "You know, Daddy, this is really nice, we have ponies and apple trees and everything, but I'm never going to learn anything out here. We should move". And, so, I started looking. And, very, serendipitously, Nancy, who had been looking at Chairs, came up to me and said, "You know, there's this job in Stony Brook and I'm the token woman, but I'm not going to get this Chair, Herb Meltzer is going to get it". Stony Brook was a new university with a very good neurology department with Bob Moore as Chair; it had superb physics with a couple of Nobel Prize winners and it had Brookhaven National Labs on one side and it had Cold Spring Harbour Lab on the other side. So, I said, "Nancy, that's the one job I would like". And, she said, "Well, do you want me to call up the Chairman of the Search Committee and say you'd look at it"? And, I said, "Sure". And, in two weeks, I had that job. They just invited me out. I gave a seminar and I got the job and we decided to move to Long Island.

AT: Had they offered it to her?

FH: I don't think so. And, Stony Brook had all the promise. It's a tragic story, because it could have been one of the great universities. It really had promise. My department had a research institute funded by the state of New York and called the Long Island Research Institute. And, that research institute had some terrible people and it had some very good people. Harvey Karten, a very exceptional neuroanatomist was there and had the resources to do some very interesting things. When I went there, the department had been run by Stan Yolles, the former NIMH director, and was very community mental health oriented. It had no real thrust in research and I thought I would try to build up some basic research. Max Fink was there. I encouraged him to really be part of Stony Brook, not Hillside. We had Wally Mendelson doing research in sleep, and Lynn DeLisi in schizophrenia. I hired Bob Hitzeman as a pharmacologist. He's now out at Oregon, a very good Chairman of Pharmacology. We had about five or six groups of people doing research that could interact, and what really appealed to me after I got there was that medical imaging had just started. The person, Paul Laterbar who won the Nobel Prize a couple of years ago for doing structural MR, was at Stony Brook at the time in the Chemistry Department. And, I went to to him and said, "Paul, this is going to change medicine completely. Would you be willing to move from

chemistry to psychiatry if I made a whole building available to you”? I had a group of sex researchers, Dick Green, Joe LoPiccolo, who were making a lot of money with infrared training movies on how to make sex and I thought, geez, I don’t really need this.

AT: Infrared movies?

FH: They had a camera, you see, so they could take movies in the dark. They were probably forerunners of good pornography. This was all educational. They had a whole building. So, I encouraged Dick to go to UCLA and Joe went to Missouri.

So, I had this empty building and I talked with Paul and he was willing to move. And, I had a grant with Al Wolfe, one of the very early PET scan grants at Brookhaven National Labs and I thought we’ll have the NMR and PET and we’ve established contact between the Brookhaven physicists and the Stony Brook physicists, talked to Siemens and got an agreement that they would give us three machines, one for spectroscopy, one for clinical structural MRI, and, a third machine for animals. Everything was in place, but Paul wanted one more position. He wanted a pharmacologist position and I didn’t have it and pharmacology didn’t want to give one and claimed they didn’t have it. So, I went to the President of the university, Jack Marburger, and Jack said, “no”! And, Paul, accepted an offer at the University of Illinois; the Beckman Foundation, within six months, gave him thirty million dollars to form the Beckman Center. He won the Nobel Prize, and I had an empty building.

AT: Did you say anything to the President?

FH: No, we had to move on at this time. I hired Nora Volkow and she was developing a very nice program at Brookhaven and I got the second round of PET grants but I sort of backed out of that and said, “Nora, that’s really your baby”. And, then, I talked with Loran Mandel, who had become the Chairman of Neurobiology at Stony Brook and President of the Neuroscience Society and said we needed to find some way to form a Behavioral Neurobiology department. At the same time, I had some ties with Cold Springs Harbor; we had one or two projects going with them and became fairly friendly with Jim Watson and it looked like we could pull everything together. So, we recruited David Amaral and Howard Eichenbaum. I don’t know how well you know the field. Howard is one of the really, really fine physiologists in hippocampal function and David is a world class neuroanatomist, and they came but their labs never got finished. And, the Provost now decided that that wasn’t his high priority, so they said if those labs aren’t finished in six months, we’re leaving. And, they didn’t finish them in a timely fashion and they’re left. And that’s when I started looking for another job. It became clear that this

university, which had so many opportunities, was not going to get sufficient resources to become really great. In addition the State of New York had decided to close the major state hospitals and the very sick psychiatric patients were flooding the streets, since there was insufficient community housing. I found myself in the position of not being able to treat the sickest patients in our community since they were all uninsured.

So I decided to look for another position and ultimately went to Germany in 1994. At that point, Stony Brook was in the top ten psychiatry departments in NIH funding. I just looked, recently, and Stony Brook isn't even listed in funding anymore. It's a real shame, because it had every element to become a great university.

There were three possibilities where to go in the early '90s. One was Stanford and I interviewed there and we got to the final part of the interview and they wanted to build a Charter hospital as part of managed care and I was very upset with managed care, at this point in time. And, the Dean and I, in negotiations, got into a real fight, which I said I would not come if they built the Charter hospital and he said I wouldn't get the job if they didn't build the charter hospital and I said, "Fine, I'm just going to stay at Stony Brook". And, they put their search on hold and, finally, internally, they decided not to build the Charter hospital and after I'd taken another job, and Alan Schatzberg took that job, they never did build the Charter hospital and I think that was the right decision.

And, then, I got a call from Harvard that, apparently, Joe Coyle had declined the Chair and would I be willing to apply. I of course would be willing but talked to Joe and he decided to go after all. So, I had no real place to go. At that time I was on three advisory boards in Germany. One was for the Dalhem Foundation, which was probably one of the most incredible foundations I've ever been associated with. It was a post-war foundation, created in Germany, to advance science and they had four meetings a year and the board included three Germans, who I didn't really know, and Jean Paul Changuex and I, and we were to pick topics. They did things from mathematics to medicine, and the meetings, were structured by a woman named Silka Bernard, who was a real genius at doing this. They were structured in such a way that you would take a field and you would ask what the major problem was in the field right now. Then, you would invite ten of the top people of the field to address the problem. Then, in that week, the group had to write a book, as a unit and that book had to be an idea about where the field is now, and where should it move? I was involved in several of these meetings. One was in depression; that is how I got started on my whole learned helplessness business. I was also involved in designing one in schizophrenia in the

early 1980s with Arvid Carlsson and Tim Crowe. I remember, Arvid and I walking around the lake and he telling me, very, very clearly, how these inverse agonists would be the drugs of choice and, now, this year inverse agonists has finally made it to the market. He had it totally figured out about twenty years before. And, these meetings were very, very good and, through them, I got to know German, so I ended up on a review panel for the Max Planck Institute and on the review panel for the Institute that I now Head, the Central Institute of Mental Health. The Chairman of that panel was Jules Angst and the first year that we reviewed the activities of the Institute, I suggested they really had to broaden it from epidemiology and do some neurobiology. This was, apparently, something Heinz Hafner, wanted to do, Jules called me up and said, "You know, you really should apply for that". And, I said, "I can hardly speak German". He said, "It doesn't matter, you'll learn German and the potential there is really, really good". And, so, at that point, I really thought about it. I had been asked to direct the Max Planck in Munich maybe five years before, but our children at that point, were teenagers and the idea of taking American teenagers from Long Island, who didn't speak German, to Munich, was impossible. So, when the kids were out of college, this next job came in Germany, and, at that point, my research had been diffuse.

AT: Would you like to say something about your research at the time?

FH: I had done a bunch of work on mechanisms in depression in those years, using the learned helplessness model, and had kind of gotten to the point where it was clear to me that pharmacology, when done on wild type animals, can give you very wrong answers. And when we used really good models, we, sometimes, got very, very different results. At the time, at the end of the 1980s, the beginning of the 1990s, one of the theories in antidepressant action was that they work through the down regulation of noradrenergic- β - receptors and we had shown that very clearly in our animal model, as well, and many others did it before and after us. The interesting thing was that when the SSRI's came out, they didn't down regulate β -receptors in wild type animals, but they did in our animals. At that point I decided to see if we could improve the animal model by out breeding animals with a strong tendency toward helplessness and animals that showed resilience and didn't develop helplessness. This may have been the most important research direction I had, because it gradually became the sole focus of what was a very scattered set of research activities. I had done work on astrocytic cell function, on animal modeling and a little of imaging, but in the early 1990s I was, mainly, dealing with managed care and I really wanted to get out of Stony Brook. I helped form a managed care company to keep the university afloat and the company

was fairly successful, but I was working day and night on a business model, not on anything to do with psychiatry. And, I realized that, as a Chairman, from now on in the United States, you're not going to do much research, you will principally be concerned with business.

AT: Did you see patients at this time?

FH: Yes, I always saw patients. I saw patients, a lot of patients, all the way through. I think I'm a pretty good clinician. One of my faults is that I collect very difficult patients, so that takes up a lot of time.

AT: Why not refer some of them?

FH: Because I get them in referral. For instance, in Iowa, in the end of the 1970s, before I left Iowa for Stony Brook, I had collected a group of patients with OCD and depression who were really difficult, essentially intractable. They were all institutionalized and we, ended up doing psychosurgery to attempt to help them. That was published in the *American Journal of Psychiatry*.

AT: Are we talking about lobotomy?

FH: We're talking about cingulotomy back in the 1970's, and I was scared to death of this. I finally found a neurosurgeon to do it. We only did eight altogether. The first one I'll tell you about. She's the most memorable. She was totally institutionalized. She was washing her hands so much they were bleeding. You had to bind them. She was a mother of three. She had been working. She was completely incapable of dealing with her children or being with her family and she was, actually, disassociating as if she had a borderline personality and that made me very wary of psychosurgery, because usually it doesn't do well with personality disorders. But, nothing helped her and I looked in the cingulotomy literature and the capsulotomy literature and I decided that probably in the cingulate gyrus you might interrupt this circuit. I mean, this was way before the imaging data we have today. And, then we made a cryostatic lesion, pretty small, two or maybe four millimetres and we did eight patients like that. And, this particular lady was a total success. Now, deep brain stimulation is coming back for just this kind of patient. After her operation, it was clear to me that she had been alleviated from her terrible anxiety, but she was still depressed and I treated her with antidepressants. We stayed in touch for fifteen years. She never relapsed. She would send me Christmas letters, always. And, she really was well. And, what we think might be happening is, you disrupt a set of circuits and you create a situation, in which plasticity is there and you've, then, got to use that to get the brain back into a state that's really stable and useful.

AT: What do you think of ECT?

FH: I always used ECT; I used ECT in Iowa, but when I got to Stony Brook, I was, obviously, much younger than Max Fink and Max was a very well known professor who he had his own very definite ideas about ECT. I, actually took his ECT course, because he simply knew more about it than I did. He really knows that stuff and we did ECT together. We did it together on very difficult patients many times and one of the interesting things about ECT is that although it's widely used, and a better treatment than anything else we have, its effects often only lasts for a little while and you get relapses. What Gerry Sanacora is currently doing, he's using cognitive behavioral therapy right after a successful course of ECT and he's finding that the relapse rate goes way down. And I think with ECT, deep brain stimulation and psychosurgery you set up the brain in a way that you can relearn how to deal with your environment, with the stressors of your life, and if you relearn that correctly, you're probably going to be okay. But, if you don't, you'll probably relapse again.

AT: Does this go back to your early interest in learning?

FH: Yes probably. The idea that brain plasticity is the key, is something that has run through the last ten years, in Germany, of my own research and we can get to that.

But, if we go back at that point at the end of 1993, beginning of 1994, I was very, very determined to get out of Stony Brook. So, I looked at this job and they had decided, in Germany that they would open two labs and that the new person could have one lab if he was interested in this and that they would recruit someone, a basic scientist involved in Alzheimer's research. So, I talked to Jules Angst, at length, and decided, OK, I'll apply for this job and when I got the job, I felt the crucial thing is going to be to find a researcher, who will go there and who will be a superstar. I have to establish, immediately, that this place is a biological force and there were two candidates, who had that potential. One was Roger Niche, who's currently the Chair in Zurich, who took Jules Angst's Chair, and Roger is one of the five or six best Alzheimer's researchers in the world. And, the other was Christian Haass, who is now a Chair in Munich. I talked to both of them and I decided we would recruit Christian. One of the reasons I decided was that his family lives in Mannheim where the Institute is. He defined the action of some of the genes that are genetic risks for Alzheimer's, the presenilin genes and he showed their association with the secretases. He and Dennis, in large part, built up the whole amyloid hypothesis of Alzheimer's disease, and I think he published, while he was with us, four or five *Nature* and *Science* papers. He, immediately, established a high quality science and that allowed me to subsequently

recruit other people to do that. And, I had a plan. I thought that the Institute needed to broaden beyond Epidemiology and include Addiction Medicine. So, I started a Department of Addiction Medicine, which was the first one in Germany. I also decided that we would become experts in behavior, because Heidelberg has an environment that is extraordinary in basic neurobiology. It's one of the great places in the world. They have Thomas Bonhoffer, who was, at that point, making the BDNF knock-outs and also Herman Bujard who invented the conditional knockout by turning off the gene with tetracycline. So, Herman was there, Bonhoeffer was there, Peter Seeburg was there and Peter has cloned almost all of the glutamate receptors and many of the GABA receptors. Further, Bert Sakmann is there, the inventor of the patch clamp and Gunter Schutz is there, who has done the most work on animal models of the HPA axis. So, I figured if we could put all these people together, we would have a basic science contingent that could build a behavioral science base to support clinical research using imaging, of patients as a connection to the neurobiology in Heidelberg. That's what we've begun over the ten years I've been there and it's worked very, very well. And, we were able to convince the German government to build a beautiful research building, which is now finished and it's probably one of the better behavioral biology buildings in Europe and includes imaging, We developed some paradigms in schizophrenia that were very helpful in showing that the problems that you see in the visual system in schizophrenia are actually top down problems in which the information processing is screwed up, coming down from the frontal cortex. Then, we worked some more on the pathophysiology of the learned helplessness model. We started looking at BDNF and neurogenesis; currently, one of the real interesting models of depression is the idea that neurogenesis is changed. Barry Jacobs, Fred Gage and Ron Duman have published theories about this and at the time that they were formulating those theories we started using the helplessness model to explore that and I came to the conclusion that neurogenesis plays no role whatsoever in the etiology of depression. I only know of two treatments of depression that won't stimulate neurogenesis. One is a drug that hardly works, so, maybe, it doesn't count and the other is transcranial magnetic stimulation. Now, when you make learned helplessness, you subject animals to uncontrollable aversive stimuli, something really stressful....

AT: Like what? I'm just curious.

FH: Foot shock is the easiest, but you can use loud noise or anything that they don't like. And, if you do it in a controlled fashion, for instance, take two animals, have identical cages with foot shock, have levers in

both, but have one animals' lever deactivate the foot shock and the other one doesn't do anything, then the executive animal very quickly learns to stop it.

AT: This reminds me of the executive monkey experiments in the 1950s when researchers determined that the "executive monkey," burdened by the responsibility of protecting his peer, suffered the most. Further research suggested that tranquilizing the executive monkey improved his health and mood.

FH: Other way around here and that's just what I proved. We did it with rats and the idea to me was, if loss of control is really a factor, then the monkey that has the control will do fine with the stressor, because he can shut it off. The other one won't and that's the way it worked. And, interestingly enough, all of them don't get learned helplessness, only maybe, ten or fifteen percent. And, if you do it right and we've spent years, literally, developing the model right, you get all of the clinical manifestations. You have changes in the HPA axis; you have changes in REM sleep. These things are sensitive to antidepressants; they don't breed as well; they lose weight, so they have face validity; they have pharmacological validity, but only ten or fifteen percent will do this. And, ten or fifteen percent will be totally normal in everything you check them in. So, what I did to check the neurogenesis in one group, give them exactly the same stress, because we know stress decreases neurogenesis and, then, look at the two different behaviors and the rates of neurogenesis in those two groups were exactly the same. So, my conclusion is that neurogenesis isn't driving the behavior. Neurogenesis is simply reflecting stress. And, some people respond badly to it; others handle it, but neurogenesis is not the issue that determines that. So, that's very recent and it's very debatable. There was in August in *Biological Psychiatry*, called, Debates in Neuroscience, and Ron Duman had an article and I had an article. He was for and I was against and we'll see how it turns out. Neurogenesis does something and, I mean, there has to be a reason that we're making new cells in our hippocampus and we're hardly making them anywhere else. And, I think it has to do with storing memory. If you think about it, bilateral hippocampotomy will render us unable to record new memories, but I could still give you this whole interview, because I'm not learning anything now. I'm sort of recalling. After bilateral hippocampotomy if I were to walk out of the room, and as charming as you are, if I were to walk back in, I wouldn't recognize you. I would start all over again. Now, if the hippocampus is just recording the new stuff, how does the brain record information, how does it really learn? It learns through connections, either strengthening them or making new ones.

AT: I see.

FH: If you're making new connections every time you take in a new piece of sensory information, how full are you going to get? Computational neuroscience says that if you have a closed volume and connections are the way you encode information, that at some point, long before the volume is filled, you'll create chaos with one more connection. So, you've got to get rid of them, so that's why we have apoptosis in the hippocampus, and we start our own neuron cycle and that's why we have new neurons. Now, I haven't been able to figure out how to cleanly prove that hunch, but Rob Malenka at Stanford has gone part way there in a very recent experiment that just appeared in *Neuron*, in which he shows that glutamate gradients, depending on how high they are, can tell a cell that is dividing, but hasn't yet decided whether to be an astrocyte, an endothelial cell or a neuron, and it may well be that by controlling the levels of apoptosis and neurogenesis, you continually renew the slate. And, so it could play a very subtle role in depression, but I don't think it's as simple as neurogenesis goes down and you get depressed. That, clearly, doesn't happen.

AT: Where would you say we are in the life cycle of path breaking discoveries in neuroscience?

FH: Oh, we're exploding right now.

AT: Are we still in infancy and how much more can we learn?

FH: The brain is so damn complex, we're not that old. We aren't even adolescents yet. Wait till the hormones start flowing, but it's all a matter of technique. Look at what functional imaging has done for psychiatry in a decade. I mean, we had no idea, really, where circuits were. What happens with an auditory hallucination? You can see it now and that has been incredible. The next step is to combine the genetic information, the molecular pathophysiology and imaging. You've got to put them together. I think that we're just at the beginning. If we're talking about research, I'd tell you about a paper, in which I'm, peripherally, involved in with people at my Institute. It's really Marcella Riechel and Tom Schultz, but it's going to change psychiatry, I think. It's just been accepted by the *American Journal of Psychiatry*.. There's a gene, GL 72; it has a bunch of names, but I'll use GL 72, which is vaguely connected to the glutamate system, in that, it affects the D amino acid oxidase, which affects serine, which is a cofactor of the NMDA receptor. And, this gene is clearly associated with schizophrenia. Four groups have reproduced that now. Yet, awhile ago the same gene was clearly associated with bipolar disorder. So, the question, then, that Marcella and Tom asked was, what is really the association? We've got two disorders that Kraepelin very clearly said were different. We've got the same gene. Is it psychosis? That's common

between the two and if you took all the patients, who are psychotic, the association didn't strengthen, particularly. And, they had really phenotyped their patients. So, they started to look. What would strengthen the association? And, it was paranoia. If patients were paranoid, then, this gene played a role, whether it was bipolar or schizophrenic in nature. So, they said, what's paranoia, really? And, they said, what's really going on is fear, this fear of something, an unreal fear, but it's a fear element and they looked for fearfulness and paranoia in higher association. And, they said, if it's really fear, what about panic attacks? There is a positive association there as well and that's what this paper says, that this one gene goes through three diagnoses and that's going to change how we think about diagnosis and what we're going to have to start to think about is, that our behavioral phenotypes are collections of pathologies that are very diverse and very dimensional. And, we have tried to put boxes around them, but those boxes are probably all wrong and that's why this argument, which I could never get into. Where is the boundary for disorder; what's schizophrenia; what's bipolar; what's schizoaffective? It's nonsense. It's a smear and it's a smear of a variety of genes and environmental factors and how they interact and they lead to the behavioral phenotype that you see.

AT: Does the DSM work?

FH: No. DSM-IV is almost a joke. They should wait for the genetics.

AT: I almost wonder why they can't have a software program that is constantly being updated. Users will be given the option of simply downloading the latest findings.

FH: Well, why do we use diagnosis? We only use it in medicine for two things. We use it so we can talk to each other and we use it so that we have an idea about prognosis. That's why we have diagnosis. If I say you have schizophrenia, I'm going to say, "Ooh, you're not going to do so well over time, probably". If I say you have bipolar disease, I'm going to say, "You could really get well". .

We're always going to create boxes, but there aren't going to be real clean boundary lines anymore, I don't think. I think there are a bunch of factors that we have clearly identified in schizophrenia and most of them point to a neurodevelopmental hypothesis. And, that's an interesting story, too, the neurodevelopmental hypothesis of schizophrenia. Actually, I think it was put together at Stony Brook by a guy named Irwin Feinberg. Now, Irwin was a sleep researcher and he found changes in adolescent schizophrenic patients that he couldn't explain. We used to have lunch together and he would try to figure it out and he decided that it was probably because something is screwed up in their development possibly

synaptic pruning. I think his paper stimulated a number of people, including Danny Weinberger, to really go after this. But, Irwin really did that. That was his idea. I think it's a collection of developmental disorders. You could smoke a lot of pot and have some genes wrong and maybe, a little bit of neuroregulin wrong and you'll get one form of schizophrenia. On the other hand, you've never smoked pot and you had a mother, who, unfortunately, had a virus in her second trimester and you've got a couple of other gene vulnerability factors and you will get another form of schizophrenia. But, on the whole, both of them have brains that didn't quite develop right and they didn't quite develop right, mostly cortically, mostly frontally. It isn't one pathophysiology; it's a collection of pathophysiologies and I think, it is for pharmacology in the future to figure out what are the genetic risk factors. What kind of pathophysiology is it? So, maybe, we can get specific treatments. I mean, if you look at the genes in schizophrenia, many of them are in the glutaminergic system; therefore, it's discouraging that the recent studies on glutamate activation through glycine D-serine have all been so negative. But, there must be a way of figuring out what kind of pathophysiology we have, once we know the genes that contribute. And, I think, that sort of thing is going to take another twenty years, probably, so I don't think we're very far along in neuroscience. I think there's a long way to go.

AT: Let me ask you another question as I marvel at the experience your wife had at Hopkins.

FH: I'll tell you a story when we're off tape about that, but you're not allowed to use this.

AT: OK. Whatabout Sol Snyder waiting thirty-five years to say, publicly, "You know this was the right paradigm". I'm wondering to what extent people overly invested intellectually, and maybe, even financially in certain paradigms slow the pace of the march of scientific progress?

FH: Well, of course. Who does science? Bright people, who are egotistic as hell? Right?

AT: Well, you're the psychiatrist. You tell me. I'm a historian.

FH: What do you think? You've seen a lot of them. Am I wrong?

AT: I wouldn't necessarily disagree with you.

FH: OK. And, there are people, who want to achieve something. So, they push their ideas and they tend to be loath to give up their ideas. Sometimes their ideas are right and sometimes they are wrong but they fight for their ideas.

In my lifetime, I've met two people in science, who I would say, "God, you're so much smarter than me that I'll just be quiet and listen". Only two, and one was Aaron Katchalsky, who was one of the people who

invented irreversible thermodynamics and he was, then, unfortunately, shot at the Tel Aviv Airport by terrorists. He would have won the Nobel Prize. The other inventor of irreversible thermodynamics did. And, the other one was T. K. Lee, the discoverer of parity. I think he got his Nobel Prize at twenty-six. Now, Lee has written a series of equations called, I think the Strain-Gage equations or something like that and they're thought to be the basis, possibly, of a unified field theory and that would be, obviously, a second Nobel Prize. And, Suella was very interested in creativity and was talking with him, once, about these equations and he said, "You know, I could almost not get them published, but I had a Nobel Prize and, so, they published them, but at the time when I published them, none of the data fit. Everything we knew about the variables didn't fit my equations, but these equations were so beautiful, they had to be true, and as we got better methods, it looks like they might be true".

AT: That's frightening.

FH: Isn't that frightening? It was the beauty; it was the beauty of it. That's how he thought, but most of us aren't able to do that, so we fight real hard for our mundane ideas and we think that each of us is great and the fact of the matter is, each of us is taking little grains of sand and putting them down on a coral reef and, once in awhile, somebody will lie or somebody will do something wrong, and that grain of sand won't stick very long. It'll fall off, naturally, in the course of time, so as science works and, once in awhile, somebody will get a grain and they'll break the surface and that person will get the Nobel Prize, like my friend Jim Watson. And, Jim will be the first to tell you some of it is sheer luck meeting a ready mind.

AT: But, what if you get so invested in your grain and you're so articulate you convince, say, a pharmaceutical company to develop a drug, based on this grain, and, it's, then, given to patients, wrong idea, but all these people stubbornly backing it, don't people get hurt? I mean, isn't there a kind of ethical dilemma?

FH: Isn't there a check and balance in my grain? If I convince the pharmaceutical company to do it, I've got to give them data on some animals; I've got to give them data on toxicology and, then, they've got to do a clinical trial. And, if they're halfway honest, it'll either work or not, might even work because of some other mechanism that I never thought of, but if it doesn't work, it should come out in the wash.

AT: So, the truth, then, is that the checks and balances are overwhelmed by the suppression of negative clinical trial data on medications?

FH: No, because in the end, if people don't get better, they're going to stop using it. Eli Robins once said to me, statistics are irrelevant in medicine if you have good medicines. Fleming didn't need statistics for penicillin.

We only need statistics because our medicines are so awful. I mean, I'm in a huge debate, right now, in Germany over the use of acetylcholinesterase inhibitors in Alzheimer's disease, which are marginally effective. At best, you win a year in the progression of the disease and they're expensive and it's a cost benefit question. Obviously, the marketing is done with enormous vigor. Now, certain countries may choose to pay it. Other countries may choose not to pay it. But, I think that people do get terribly invested in things, and money and power make them do very dumb dumb things sometimes.

AT: Let me switch back to another topic. Do you think it is harder for women to break into the field? You don't see of many of them in the ACNP.

FH: I think it is harder. I, obviously, have a soft spot for women. Stony Brook had a group of women professors and they were really good. In Germany, I decided that I would create the first woman professor of psychiatry. There's never been one and I took a woman, who's really tough and can be nasty, but I figured she'd have to be. It was the hardest fight I ever undertook. I could not do it, although she clearly deserved it, academically. She's very competent. It was, eventually, accomplished politically. I'm not bad as a politician and I knew someone in the administration and I said, you should put some pressure on; this is a real issue, the other candidates are no better and it's time for a woman, and they did it. But, now, the second woman has a Chair in Germany and it is opening up. I think it's much harder, sometimes, for women. It's harder for minorities. It's like everything. It depends, partly, on your connections. If you come from Hopkins or Harvard or Cal Tech or Stanford, you've got a great chance, compared to somebody coming from Kansas or Omaha or God knows where, and it's just because of who you know.

AT: Final question and, then, if you have anything to add, please do.

FH: God, I've already added everything.

AT: For someone just entering the field, what pearls of wisdom would you share with them? I ask this, pretty much, of everyone. No one said, run away, go back, yet.

FH: No, I wouldn't say, run away, go back, but I would say that if you want to go into research you have to love it. You have to be obsessed a little bit with it, and if you're not, then, think about something else, because it's a pretty tough mistress and the rewards are fairly limited. I mean, nowadays, with biotech, that may not be true anymore, but it used to be. But, I think you really have to love it and that would be the thing. I once had a very funny development. Henry Eyring was a famous physical chemist. He was a Mormon and, as a result, was a racist and that probably kept him from winning the Nobel Prize, because he openly stated his beliefs.

For some bizarre reason, he was at the University of Virginia, doing some sort of sabbatical type thing, and he used to have a lunch time seminar. I was trained as a physical chemist, so Henry Eyring was god to me and I went to this seminar. And, we started to talk about membranes; I had just finished my PhD thesis on Black Lipid Membranes and I had worked out a crazy theory on what the Hodgkin-Huxley equation actually meant. It was totally wrong, but it kind of fit the facts, almost, and Henry and I got to talking about this over lunch a couple of times. And, then, I, actually, showed him the map. I mean, I, actually, showed him what I had done and I thought it was a bit of a joke. It was almost a game with me and I forgot about it, and about four months later, *Science* comes out and his presidential address is this theory. And, there's a footnote of people he thanks, in type so small you need a magnifying glass, and in the middle of that, I'm listed.

AT: No attribution to you in the text?

FH: None, nothing. And, I was furious not because he'd done it to me but because I thought it was probably bull shit. He was still in Virginia, so, I went to see him, and sputtered, "How could you do that without asking me"? And he told me to calm down and he said, "Well, if you want a career in science," and he was an older man, "Let me tell you something. You're not totally stupid. You seem to work hard and those are important qualities, but what you've just learned here, you've got to have gall, boy; you've got to have gall". And, he took me to the door.....

AT: Another good lesson for the young.

FH: Yes. So, it's been a very interesting scientific life.

AT: And, it's not over yet.

FH: No, hopefully not. We'll see.

AT: Good luck to you. Thank you so much. That was really great.

FH: God, I just chattered away.

AT: That's wonderful.

LEWIS L. JUDD

**Interviewed by Andrea Tone
San Juan, Puerto Rico, December 9, 2003**

AT: My name is Andrea Tone, and this afternoon I am interviewing Lewis Judd.* It is the 42nd Annual Meeting of the ACNP in San Juan, Puerto Rico. Thank you for coming.

LJ: Good to be here.

AT: Why don't we start by having you tell me a bit about your basic background, where you were born, a little bit about your upbringing and early education?

LJ: All right. I was born in Los Angeles, CA. Do I speak to you or to the camera?

AT: Either. Some prefer camera. Some prefer me. For a better interview you should probably look at the camera.

LJ: OK. I'll look at you periodically, for reassurance. I was born in Los Angeles, CA, and was raised there. And I had my primary school and secondary school there. I was in prep school in Los Angeles. And then I went to the University of Utah and graduated in psychology, a bachelor's in psychology, and was debating whether or not to go into psychology for a PhD. or into medicine. I should have mentioned that I was raised in a physician's family; my father was a prominent obstetrician gynecologist in Los Angeles, basically in private practice, but taught at the University of Southern California in his specialty. He was also active politically in the sense of medical politics. He became the president of the American College of Obstetrics and Gynecology in its early being. So I was raised in a physician's family. You know, my father's activities and profession were really paramount and central in our lives. And I think all along I probably harbored the idea that I would want to be a doctor, but it was, in a way, it was a bit of a tough act to follow. So, I thought about maybe branching out on my own and into something else. Yet, when the choice point came, I chose medicine. And I've never regretted it. It's been very good.

AT: Going back a little bit to your days at Utah. You graduated from the University of Utah 1954. What drew you to psychology as a discipline in the first place? And can you tell us a little bit about the approaches, the intellectual schools that were presented in the classroom in the early 50s.

LJ: Sure. I was trying a lot of different things at the time. I thought I might become an English-major. I did so take pre-med courses. And, then I hit

* Lewis L. Judd was born in Los Angeles, California in 1930.

on psychology, and it was a very good fit for me. It was something that I could do well. It was something that I found very interesting. I was particularly taken by physiological psychology, which really was the forerunner of neuroscience. Right now physiological psychiatry and neuroscience are indistinguishable in our field now. This was the biological basis of human behavior, which was very appealing to me. It made a lot of sense. It was not as ineffable as some other aspects of psychology, which are more philosophical and artsy-craftsy in their approach. This was definitive. Here was data. Here was explanation that made sense. And so I did quite well in physiological psychology and was offered a position to join the graduate program there. But I decided not to. In retrospect, I can tell that I was being tracked; the teachers were passing me on from one to another with the idea that I would then stay on in graduate school. So that did appeal to me very much. So did the more scientific end of psychology. And that's why I chose medicine. I went to UCLA's school of medicine; in my own hometown. It was a brand new school at that time, one of the first ones started after the last war, and it hit with a bang. It was, almost overnight, a first-class medical school. It had the largesse of California behind it. They went and got full departments from other universities and brought them to UCLA. And so it was a very heady time to be there. Classes were small. We had this magnificent facility in which to be, and there was a lot of focus on us as medical students. We weren't an afterthought. We were a primary focus of interest for the faculty. They really spent a lot of time with us. They tracked us very well. There were no grades. It was one of the first schools to have no grades. You went through and if you did fine, you did fine. But we were soon able to discern who was doing better in the class because they would take the top five students for a special interview with the dean at the end of the year. It was a very unique time to train in medicine in a medical school that was new and was really feeling its oats and was on the make. And so it was very important where we took our internships because that would define how well the school was being accepted. When I graduated from medical school I graduated with honors, I and some of my friends did have options to go to the most prestigious internships. And some did. But one very close friend and I decided that we were going to stay at UCLA in medicine. So, I stayed at UCLA in internal medicine with the idea that I would definitely go into academic medicine of some sort. So rather than go into a practice, and develop a large practice, as my dad did, my decision was to go into academic medicine. I was leaning toward that strongly. Now, during medical school, we were honed to go into academic medicine. In retrospect I can see that. I also did research when I was in medical school.

AT: Was that typical?

LJ: I would say more of us did than not did. We had summer internships in research. And, since my dad was in obstetrics and gynecology, I worked with a guy named Nicholas Atchley who was a brilliant, brilliant renal physiologist and OB/GYN man. He was one of the first people to work in the toxemia of pregnancy, and one of the first also to do the basic physiology in high-risk pregnancy, in sheep. I worked with him for several summers; another fellow medical student and I conducted what was rather fundamental clinical research, in toxemia of pregnancy in which women will develop a shut down of their kidneys, begin to retain sodium, their blood pressure goes high, get very large, and put on weight, a lot of water weight. Toxemia can be lethal; the patient can go into convulsions, etc., and there was very little to do for it at that time, except to put women at bed rest. So we admitted these patients and put them on bed rest. That worked for some, but it did not work for all. We were, with Nick's direction of course, the first to give them a drug called chlorothiazide, which is a diuretic, and study their electrolytes; looking at their sodium, potassium, and various things like that. We would arterialize their blood, by wrapping their arms in hot packs so that the venous and the arterial blood, becomes more similar; and we would take the blood to the lab and analyzed it. And it turned out that this drug was rather magical in the treatment of toxemia in that the retained sodium was excreted and patients got better. We then helped to analyze the data, and wrote up our findings. I was the senior author on two of three papers. One was published in the *Journal of the American Medical Association*, which is a high quality journal, as you know. Another was published in the *Journal of Clinical Endocrinology and Metabolism*, which was another high impact journal. So I got my first taste of research there.

AT: You were already published by the time you graduated from med school.

LJ: Yes, I was.

AT: And this had a huge impact.

LJ: Of course. Well, it did. But ultimately I chose not to continue with that research that I should not be earmarked for a career in OB/GYN, especially by those who knew my father. Even the medical school was pushing me into OB/GYN in the sense that at that time and maybe even now, the cream of the crop went into internal medicine, and the remainder into other specialties. Now in psychiatry and neuroscience we are getting great people; there's no question about that. . But at that time, this was not the case. So the Dean and people were saying, well, look, you know, you could have a brilliant career in obstetrics; you know, there are not that many really good people going into it; you know, you'll be one of a group

of very good people in the field. Internal medicine is kind of the queen of the specialties in medical school; it draws the best students usually. So, I had published three papers by the time I graduated, and I actually presented a paper at the meeting of the American College of OB/GYN. I had never presented a paper before. It was an interesting experience, because I didn't know what was going on. You know, when you got to a certain number of minutes of your time in your talk an orange light would go on; then there was a green light, and then there was a red light, and if you went over time with your presentation the light started blinking. And I didn't know what the hell was going on. But, I went through with my talk. So, then, I went into internal medicine at UCLA.

AT: Can I ask you about your exposure to psychiatry in medical school? You graduated with a BS in psychology, and yet you elected when you entered med school not to pursue a psychiatric track.

LJ: No, I elected not to be a psychologist. I elected to be a physician, and I did consider psychiatry. That probably was preeminent in my mind when I first went into medical school. I thought, well, you know, psychiatry will be a good specialty for me. Now, UCLA was very unusual at that time. They integrated the teaching of human behavior, normal and abnormal, right into the teaching of pediatrics, medicine, surgery, etc. So we had a very thorough grounding. I mean, their effort at that time was to make us humanists; to make physicians like physicians should be, well versed in things, understanding the patient, comfortable with both normal and abnormal behavior, able to recognize abnormal behavior, and treating a patient as a total person, and not as a set of symptoms. We had psychiatric teaching going on that was integrated completely with our other courses, all along. So there was no stigma against psychiatry. You know woolly-headed, bearded Freudians, and their couches; there was none of that.

AT: So there was no psychoanalysis.

LJ: It was there, but it was highly respected, and it was part of medicine. So I grew up with that ethic and with that value system; it was unlike now. I mean, it was light years away from now. We were very much grounded in psychiatry; we had superb courses in psychiatry. And we had a couple of very charismatic teachers that were really wonderful, just absolutely first rate human beings, very insightful. So, I had a very positive feeling about psychiatry, but I was drawn to medicine. I think mainly because of an elitist drive. And, then, at the end of my internship year, I began to notice in the clinics that many of the people that I was seeing had psychiatric problems that were complicating their medical illnesses. Medical illnesses and behavioral problems were mashed, in a sense that you really

had to deal with both. In order to get the patient to be compliant to take the medication, to comply with the regimen that you outlined, you had to have an alliance with the patient. So, I decided to take a year in psychiatry at that point to help me with internal medicine. It really bothered a lot of people in the medical school. They felt that they were losing a very good student to what they felt was not a premier specialty.

AT: So, why did these people have this bias against psychiatry at that time?

LJ: Well, there still is a bias. I mean, there is an age-old stigma of centuries against mentally ill people and against people who take care of them. Plus, also, psychiatry was not a very scientific discipline; it has only emerged, really, in my lifetime as a scientific discipline. It wasn't a scientific discipline at that time. And so I had a number of lunches and dinners with senior professors, and especially neurologists, at UCLA trying to talk me out of this. They would say come into neurology. You can do the same thing. You're going to be lost in psychiatry. In those years psychoanalysis controlled psychiatry. There is no doubt about it. And there was a big dose of it. Dynamic psychiatry is very useful in understanding human behavior. It is. So we were using it. There were only a few isolated biological findings in psychiatry as for example phenylketonuria, an inborn error of metabolism in which there is a gene missing that metabolizes phenylalanine, and this has a profound effect on the person. You end up completely retarded within a few years. It was very impressive to have an identifiable physical, metabolic defect that can make a young, growing baby demented. And as a result of those few isolated findings we began to get a sense that there are other things going on besides the ego and the id and that sort of thing. Anyway, although they tried to talk me out of it, I took a year of psychiatry. At that point, I got taken into the Air Force. It was a time when a group of us had signed up for a thing called the Berry Plan. The Berry Plan allowed you to finish your residency and not be taken into service; there was a doctor draft still ongoing. So a lot of us joined the Berry Plan with a guarantee we would be able to finish our residency and perhaps never go into service. If you weren't needed, you didn't go in. But at the end of my first year, the armed forces ran short of psychiatrists. So a group of us who were single, even though we only had one year of psychiatry training, were taken into the service, and then we were assigned to the three different branches: Army, Navy, Air Force. I was assigned to the Air Force. And so I went into the Air Force as a psychiatrist.

AT: After one year.

LJ: After one year. And I'll tell you, I was an expert compared to the people around me. They didn't know any psychiatry. I was flying blind at that time but I felt quite confident to handle what was there.

AT: What was there?

LJ: I was assigned to a regional hospital in upstate New York at a base called Griffith's Air Base, which was a huge air base that had a strategic air command wing and had air defense command wing. Rather than creating centers around the world, which they now have, where they can be repaired, or even on site to some degree, all the ground-air electronics for the entire Air Force were repaired there. They were trying to save money by doing it this way. It was a huge base with 25 or 30 thousand people. It had a hospital, a regional hospital that drew from the northeast. And I was the psychiatrist.

AT: For the whole base?

LJ: For the whole region. And so I had a very active outpatient practice in terms of doing lots of consultations for the other physicians in the hospital. Lots of people sent to me by the commanders on the base, you know, people who were having difficulty and problems. And I also ran an inpatient service. So when people had to be hospitalized, I hospitalized them. And I would always have one or two people in the hospital, sometimes up to 10 people in the hospital. I was getting all the DTs, the alcoholics who were having withdrawal symptoms, and I was taking care of them. They were sent to me. So I was very busy.

AT: Did you feel at the time that there were mental health issues specific to individuals in the military?

LJ: Oh, sure; absolutely. There were a number of things that I did try. For example: the Air Force has aptitude tests when you go in, and depending on your score on these aptitude tests, you were tracked into various jobs. People with the highest aptitude scores went into areas with high technology, photography, intelligence. The amount of technology in the Air Force even at that time was immense. There were missiles and that sort of things. Then, people who were not very smart were sent to be cooks; and people with the lowest scores were sent to the Air Force police. Often, we had very troubled people who were having a hard time adapting to the Air Force. If you think about it, going into the service is an enormous stress. You go in, you leave your family, and you leave your friends. You go in and you're living with a bunch of guys. It's a male culture and it's very tough. You're put through a lot of physical demand. You get very little sleep. You are learning a lot. It is about as much stress as you could put someone into, and a lot of people would break down. A number of them would break down and have psychotic reactions. One of the best places to study first onset schizophrenia is in military hospitals.

One of the things the Air Force police did it was guard the B-52s because a lot of people had psychotic reactions at night. We had always

five B-52s ready to go within ten minutes; the pilots and the crews were in the alert shack, nearby. And there was always one plane from our base in the air flying missions to the Soviet Union. When we had the Berlin crisis we had more than one plane in the air at times. So these Air Force police guys were out there by themselves with their guns in the cold, and this was in Rome, New York, which is bitter, bitter cold, well below zero. They're standing out there for four hours before they would be relieved. And some of them began hallucinating. A couple of them shot their guns off and things like that. So, I said, let me do an experiment; let me put a heater near them and a light; let us have people to come and talk to them periodically. So we did that for a few nights in a row, and it was magical. I wanted to write it up but was told I should not. It was implemented, but who knows if it went beyond the base. There were, a number of little things like that I was involved with. . So, anyway, I had a wonderful education in psychiatry in the Air Force. I saw hundreds of patients. I took care of everything. I saw everything. In retrospect, I did a fairly good job. It was a good clinical experience; I was working long, long hours,, and saw all kinds of patients. I saw people paralyzed, hysterically, and I would treat them, and they would get up and walk and go back to work. You see in the service some things you don't see elsewhere. You see hysteric who can't walk, hysterics who are blind, can't talk, and this sort of thing. It's because of stress and they don't know any better, so they express their stress in this way. But, anyway, it was a great experience.

AT: Were you implementing some of the new drugs?

LJ: Yes, absolutely. Then I came back to my residency. That was really funny because I was far more experienced than the other residents in the class, and more than a lot of the junior faculty. So, I decided to do something different, and I went into child psychiatry, at that time, child and adolescent psychiatry. So, you know, I had a very good training. And I had no thought about going back to internal medicine. It was done. I was on my way. So I went into child psychiatry.

AT: Child and adolescent psychiatry?

LJ: It was to balance my education and my expertise I took another period of the life cycle. And I did it also because there was, and there still is, a very strong hypothesis that the disorders we are dealing with in psychiatry are developmental in nature. Certainly in bipolar disorder, we're looking very heavily into adolescent onset, and even earlier onset. So, I felt it would be worthwhile, if I had two years of residency in child and adolescent psychiatry. And I got very interested in adolescent psychiatry at that point, and became, quasi a local expert in it.

AT: How were adolescents different from adults?

LJ: Well, they tended to be extremely difficult patients; heavy denial and a lots of acting out. They convert their illnesses more to behavior, often dangerous behavior. And I prided myself in being able to take care of very difficult kids that no one else could take care of. So I saw a lot of those during this time. I'd taken care of two young kids with severe, obsessive-compulsive neurosis, as they called it at the time. And the kids were ravaged by it. They were washing their hands hundreds of times a day, so that their hands were raw and bleeding. They could not touch the door-knob and they had terrible contamination fears. I was really impressed with what I saw and did a survey of the literature. Then I looked up all the records of kids at UCLA with this illness; there were only five since the time the institute had been opened. Then I looked for common features in the cases. My paper on obsessive-compulsive neurosis in kids was accepted for publication in the *Archives of General Psychiatry* by return mail. That never happened to me again. Now, at that point, I went on the faculty of UCLA. They invited me to stay on the faculty, and they asked me to establish an adolescent psychiatry clinic that I did. It may still be going. I don't know. So I worked in adolescent psychiatry and in child psychiatry while I was at UCLA. I knew so, that if I were going to be successful academically I would need to engage in some serious research. As a young faculty, I wanted to get research training, which was not common at that time, and I thought the place where people know design, methodology and statistics is in psychology. So I went up to the Department of Psychology at UCLA and I found two unique people there to work with. One was Elliot Rodnick, a very gifted experimental psychopathologist, who was using experimental technique to understand psychopathology. And the other was a guy named Michael Goldstein, who was a superb scientist and a member of this college. Unfortunately, he passed away a few years back. Elliot, Mike and I were looking at high-risk kids for affective disorder and studied family interactions. Mike and I were interested in psychopharmacology, so we did some very crude studies in psychotic patients. In one double blind study with neuroleptics we would look at changes in galvanic skin resistance and not only symptoms. In another, we would expose schizophrenic patients to word association tests to document the effect of neuroleptics on their idiosyncratic responses. We were interested to find out which medications would correct them. And I then got interested in genetics. At that time genetic research meant chromosome analysis. So I did the first chromosome analysis in schizophrenia; it yielded negative findings. I did also a chromosome analysis in children with primary infantile autism. I thought we'd find something, but we didn't. And then I got involved in looking at chromosome fragmentation

with LSD. Although I was very early into genetics, I didn't realize its future importance. I was also using a wrong technology. By that time I had been offered various jobs around the country to head divisions of child psychiatry and things like this, and I was also offered a job with a friend of mine at the University of California - San Diego to start a new department of psychiatry. It seemed like a great opportunity. Psychiatry in those years was changing very fast. As we were changing in our research, the whole field was changing.

AT: In what way?

LJ: It was becoming much much more empirical. It became very clear that the brain was the organ system of interest, and as more we learn about the brain, as more we would know about normal and abnormal human behavior. So it was becoming a scientific field. Psychoanalysis was slowly left behind as neuroscience at a cellular and molecular level began to grow. It was the fifth psychiatry department in California. The other departments were in San Francisco, Los Angeles, Irvine and Davis. UCLA and UCSF had a great advantage; they had money from the state department of mental health. By the time UCSG was established the money dried up. So, we were kind of on our own. So we decided that we probably should not be a big department, but we wanted to be a department of the future. So we made a very big investment in basic neuroscience in our department and in basic neuropharmacology, and also to some extent in clinical pharmacology and behavioral pharmacology, at a time when very few departments were doing that. And it proved to be prescient, and it proved to be right. I was the Co-chairman of the department with my friend, a guy named Arnold Mandel, who was the Chairman, and for the first four or five years we tried to get the department going. It turned out that Arnie was a brilliant guy who had a real vision of the field, but he was a bit erratic administratively. You need stability, especially in a new department and it turned out over time that I was much better in providing stability than he was. So we kind of divided things up. I would run the department on a day-to-day basis and he would do his research and come in whenever necessary. And that's the way the department started. Some people left and some others came and within a few years we were stable because I had my hand on the helm by this time. It is difficult to run a department and maintain a major research career although there are some people in our field who have been able to do it. So, I selected a fairly narrow area in which I have remained involved in doing cutting edge research. In this way I've been able to maintain a research career despite being a chair and despite being director of the National Institute of Mental Health for a few years. .Before I went to NIMH, I was primarily looking at

drug effect on behavioral mechanisms in my research. We were first to look at the effects of psychoactive drugs in the normal person. Prior to us people only studied the effects of single doses. We were the first to put normal subjects on therapeutic doses of lithium for a period of time, chronically, so you really knew what its effect was. And so we published a number of papers on that at that time. We found that lithium had a central slowing effect on cognition. We were also interested in the effect of endogenous opioids on psychopathology, and on normal human behavior. We did a number of studies using naloxone and methadone in low doses to test this out. We thought we might have a marker at one point, for depression but it didn't work out. We also thought that naloxone has an effect on manic behavior which in a large multi-center study did not pan out. It was a negative study. But we did notice some changes. All these studies were double blind and videotaped. In another study we tested the hypothesis that lithium can calm down mania but would not have an effect on the euphoria generated by certain drugs, e.g., alcohol, cocaine. We did a series of studies and found that pre-treatment with lithium had dampening effect on experimental intoxication. Our findings led other people to study lithium in alcohol and alcoholics. The department had evolved in such a way that it was getting a lot of attention.

AT: When was that?

LJ: This would be in the 1980s. We always were recognized as a good department, even though we were younger than other departments; we were 5, 6, 7-years old, when other departments had been in business for 50, 60, or 70 years. Very early we made a splash. We had very strong neuroscience, and with a grant from NIH we became one of the early mental health clinical research centers.. They put out only 11 grants, and we were one of the 11 grantees. I was getting a lot of offers to go to other places, but I was quite happy at UCSD, and decided to stay. And, then in 1986 or 1987, the director of NIMH left, and they formed a search committee, and the rumor around the country was that I was going to be one of the major candidates for it. So one day I was talking to the Chancellor of our university, and he said, hey, I hear that you could become director of NIMH. I said, I don't know, I've not been told that I'm a candidate. He said, why don't you do it? Go and get it. So, I talked to the President and I talked to the Governor and I was told that they will keep my job open here if I get it. So I said, okay. So I then went and interviewed seriously at NIMH. I went there with an idea of what I would like to do there, with my vision of the NIMH, what it should be, and what it could be. And because I had interacted with the Institute, all through my professional life I had some very definitive ideas of what it could be, but what it was not.

AT: In a nutshell...

LJ: It should unabashedly be a scientific institute. That was its only business. It had not been at that at the time. It was involved in training. Secondly, it ought to be a leader in the federal government, and the nation, and the world for neuroscience research. We were being dealt out of the action there. Neurology was taking it over. Other institutes were taking it over. NIMH was being pushed out of basic research. The guy just before me was told from the Hill: Don't do basic neuroscience, that's for the other scientific institutes. You do the behavioral research. I also thought that it should hire the best and the brightest people and that it should have a role in stimulating the field, the science of the field. I presented these ideas and I was offered the job. And I went, and they kept my job open at UCSD. I was there for three years. It wasn't quite long enough. I really changed the Institute in a major way.

AT: When you left, what would you say your achievements were?

LJ: Well, one was that we became the leader in neuroscience. We pushed and helped to orchestrate the Decade of the Brain. Many people have said I'm the architect of the Decade of the Brain. That's not true completely. I did have a lot to do with it. I had a lot to do with implementing it. A guy who shepherded it was Silvio Conte, Congressman Conte. He was a buddy of mine. In fact, I was the only scientist institute director when the Decade of the Brain was signed. The architects of the Decade were Dominici, Conte, Lou Sullivan, who was my boss, and me. I went to a meeting of the Association of Neuroscience Departments and Programs, which is the place where all the neuroscience graduate programs gather, and when I made my presentation, the president got up and said, you know, it's real clear that the leader of neuroscience in the federal government is the NIMH. Plus, we also, we initiated four general national research plans to organize the field of research. One was the Decade of the Brain research plan to really put us on the map in fundamental neuroscience in the broadest aspect. Another was the schizophrenia research plan. The third one was for child and adolescent disorders, and the fourth for the severely mentally ill. So that set the table for NIMH research until the end of the last decade. We carved out our program with 50 to 60 new requests for proposals that laid the whole thing out.

AT: You have done so much administratively that has really shaped the field. What would you say, in looking back, your key research contributions have been, or how do you feel that you left a mark that distinguishes you as a scientist?

LJ: Well, I think that probably my best research is ongoing now, over the last seven or eight years. I was very affected by being at NIMH. NIMH

is responsible for all the science in mental illness, but also is responsible for setting national policy in mental health. And so I was very taken by the intense public health need that mental disorders present. Right now, mental illness is the most important under met public health problem in the world in both developed and undeveloped countries. This is established very, very soundly. Not by people in the field, but by the World Bank, by the World Health Organization, and other organizations. In my research I wanted to do some things that would influence the treatment of people and would be helpful for clinicians. It has taken two directions. In one, we have defined in detail the lifetime course of unipolar and bipolar depression. It had never been done prospectively. And I'm involved with a group of people in the collaborative depression study that NIMH started in 1978. It has been ongoing since that time. A huge number of people with mood disorders were followed systematically, regularly, proactively in great detail for over 20 years now. We have been describing the course of illness. And, one of the things we contributed to is that depression is not an acute illness. It's a chronic illness. It takes its course across lifetime. We also have been studying the disability associated with it, because of its public health importance. And we have been able to show that the people with unipolar depressive disease are ill with their disease 60% of their lifetime. They are asymptomatic less than half of their lifetime.. And when they are asymptomatic, they are not disabled. When they are symptomatic at any level, there are grades of disability. I think this is of fundamental importance. Since depression is a chronic illness, we are looking at something that we think will distinctly change the chronicity of the illness. We found that if someone has a depressive episode or a manic episode, and they get completely well from it, regardless of how it happened, the likelihood of them having another episode quickly is very low. In fact, they will likely have far less episodes in the future and will be far less time symptomatic. If you recover from the episode and you no longer meet criteria for major depressive disorder or a manic episode but you're still symptomatic the likelihood of your relapsing quickly is very high and also that you're having a very chronic, less benign lifetime course. What we don't know right now is, is this defining two populations of mood disorder patients; one group that can get really well and another group that don't and bumble along the rest of their lifetime. It's really clear that when you get someone from this group and ask them are you completely normal and well they say, you know, not quite. I'm really better, but there is a little this, that, and the other thing. But then there are those from the other group, who say, yes, I am completely well. We found that's a state of stability, and they will stay that way for a long time, until environmental or endogenous stresses, cause a relapse.

- AT: Thinking about psychiatry when you entered it and psychiatry now, what do you think the key changes have been?
- LJ: You know, it is an entirely different field now. It is not the same field. It really is now a scientific discipline. It was not then. It was an art form, an intuitive art form. Now it's a scientific discipline. You know, treatments and diagnoses are evidence based. We demand it. We have more to offer than ever in our history, without question. We can manage most mood disorders. Think of that. Well, a bipolar patient 50 or 70 years ago would spend 25% of the time in a bipolar episode, manic or depressive, 25% of the time going into it, 25% of the time coming out of it, thus 75% of their lifetime was probably in a hospital. And that's not true at all now. We can offer a great deal. Our field has changed more than any other in medicine, without question.
- AT: Where do you think it is going? I mean, if you could look into a crystal ball, where do you think the treatment of the mentally ill in this country will be, say, 15, 20, 25 years from now?
- LJ: It depends on major discoveries in genetic research. Although, it is very hard to go from the gene to a treatment, we have had evidence for this with the genetics of Huntington's disease. I think the answer to your question depends on progress in genetics. We are going to be conducting genetic medicine, probably not so soon, because our diseases are very complicated scientifically. Take a disease like schizophrenia; until 25 to 30 years ago you could not see any difference in the brain of a schizophrenic from a normal person. And yet, schizophrenic persons are so disabled that they're eating out of a garbage can, and they're living on the street. So, whatever the change is in the brain, it is amplified enormously from the brain into the behavior. And patients with schizophrenia will never be the same. They're just going to get worse or, at best, stay the same. You know, if you have liver disease, you can take a biopsy, and say, whoop, there it is. You could biopsy the brain all over in schizophrenia a number of years ago, and you could not find any difference from the normal brain. So we are dealing with an extremely tough problem because the schizophrenic brain merges with the normal. The difference is dimensional and not categorical. So, in any case, I believe that we can take a major short cut with the genes, if we can really find some genes which can direct the scientific inquiry into how to correct the abnormal proteins and the deficit proteins that come from the DNA. I think that will help with diagnosis. It would revolutionize diagnosis because there will be people who don't look the same phenotypically, that may have the same genetic underpinning. So, I think this is where it's going to go. We are going to make a lot of inroads in imaging over the next few years. But right now, until we get

into spectroscopy and things like that, imaging is really just observational in nature. We're finding out how the brain functions, how people remember, and what parts of the brain are involved in learning and memory. All those things are very important. But the fundamental aspects of these illnesses, I firmly believe, are in our genetics.

AT: How optimistic are you about the future of drug developments for treatment?

LJ: I'm very optimistic. As closer we get to the genome, the better the drug is going to be. I firmly believe that drug development is going to be genetically directed. So I'm very optimistic.

AT: Let me ask you if there's anything that I didn't ask that you wanted to add?

LJ: Gosh, I don't know. We have still 5 minutes, right?

AT: Well, we can take another 15 minutes if you want.

LJ: Do you have any questions?

AT: One of the striking things about your record is what a renaissance scholar you've been. You were even on a panel on pornography and obscenity. It's interesting, because you were characterizing your early educational interests as one in which you wanted to be a well-rounded individual, and that you felt that the best doctors were those who were trained in an integrated way. Your own scholarship has reflected well-roundedness as well.

LJ: Well, I think that I've done a fair amount. I was head the head at NIMH; I had training in general psychiatry; and I have been a committed kind of researcher on a part-time basis all along. I know a lot about a lot of different things. I have had training. I had psychoanalysis early on in my residency. I didn't finish, but I had my own analysis. I know what it's all about. I don't do it. I use it a lot in interacting with people in my faculty and things like that. Plus, also, I had a flair for administration. I can organize things well. I can unite people well. I can develop consensus well. I can make people feel good. I can make ambiances in which people work to be very positive and very salubrious. So I was able to grab hold of the Institute, which had defied every director in 40 years, and make it my own within a couple years. I really was able to. As a director, you're the boss. What you say goes. People got to do it. It's like the army. I remember when I first got the Institute we had a meeting of the senior people, and there was kind of a tough issue, whether we should eliminate a program. And I said, now, we're just going to talk about it. I was used to do this in the university. We talk together. We discuss. We try to arrive at a consensus. If we cannot, I'll make the decision, but I would prefer consensus. And within a couple of days, I got several letters of inquiry from

senators on the Hill. We understand the director is doing blah-blah-blah. And, you know, that was common practice when I arrived. It wasn't any longer when I left.

AT: Then you were saying how important it was to have the 1990s ear-marked as the Decade of the Brain. What do you think the accomplishments were by the end of the decade?

LJ: Well, there have been monographs written on it. I think, first of all, the neuroscience field at the beginning of the 1990s was one of the fastest moving fields in all of life sciences.. What the '90s accomplished was to establish a phenomenal infrastructure of neuroscience research that is this incredible engine and that is just pumping out stuff right and left. I would say the discovery that, 45% of the genes are involved in regulating the structure and function of the brain; that the human genome is extremely important to neuroscience; and the importance of the development of all the imaging technology. In the early 1980s, you couldn't look at the human brain while it's in the process of functioning. You can do it now routinely. It's done every day in dozens and dozens of places around the country. I mean it's hard even now to say what was accomplished by it, because we're still learning what is human consciousness and where is the seat of the soul. I mean, these things are all becoming possible, and some of the antecedents of it were laid down during that decade. It has set neuroscience as the most unique science of man. It has set the human brain, at the highest priority of the federal largesse. It did for neuroscience what the war on cancer did for cancer research.

AT: Looking back, do you have any regrets?

LJ: You know, I have to say I really don't. Maybe I wish I had stayed with genetic research. Had I known what was going to happen, I probably would have. But actually the fact is that most of my contributions have been more in institutional building and less in fundamental research. It's been kind of an amalgam. But I did influence the NIMH, you know, in the federal government. I thought it was so well established before that I could go away and it would always remain that way. But it changed. I believe that I am in the process of developing what will be a unique department in the history of psychiatry in our field. It is really an unusual place. Not only high powered and great science, but it's a great place to be, and it's a great place to work. And people are good to each other. It's not back biting, even though it is a very competitive group of people. We have an ambience there that people can really grow in and feel safe and this sort of thing. So, I'm not done with that.

AT: We should probably wrap it up there.

LJ: All right.

AT: Thanks so much.

LJ: OK. I hope that it was useful.

AT: It was very good.

JOEL E. KLEINMAN

Interviewed by Elizabeth Bromley
Waikoloa, Hawaii, December 11, 2005

EB: This will be an interview for the Archives of the American College of Neuropsychopharmacology. It is December 2003. We are at the annual meeting of the College. I'm Elizabeth Bromley. We can start by you telling me your name.

JK: Joel Kleinman.*

EB: And, where were you born?

JK: Alexandria, Louisiana.

EB: Oh! Is that a small town?

JK: It's a relatively small town.

EB: And, tell me about your family, the family you grew up with, grandparents, siblings.

JK: I'm a third generation American physician. I was raised in Miami Beach. I have a sister and I had a half brother; he passed away. My father died when I was a young kid. My parents were separated then divorced when I was four. I was raised by my dad until I was thirteen. And, then my dad died and I went to live with my mother.

EB: In Miami Beach?

JK: Yes.

EB: Is your sister older or younger?

JK: My sister is three years older and is married to a hematologist at Vanderbilt.

EB: So, your father's death, must have really affected your junior high and high school education?

JK: Yes, that was a very difficult time.

EB: What was your education like? Did you have special teachers or mentors?

JK: I can't recall any of my teachers from that time. The person that was most influential in my education was my dad. And when he died that was a terrible loss for me.

EB: Can you tell me how he was influential to you?

JK: He was a Hutchins' whiz kid, if you know what that is; these were very young people admitted to the University of Chicago at a very early age. So he was a very bright man and he spent a lot of time to make sure my sister and I were educated properly.

EB: What kind of a physician was he?

JK: He was a GP, but he did rehab medicine. My grandfather and father had moved to Miami Beach in 1946, after World War II and they built a clinic

* Joel E. Kleinman was born in Alexandria, Louisiana in 1948.

for elderly people who were recuperating from strokes and heart attacks, in South Beach.

EB: That must have been a new thing for them.

JK: Yes, it was a pretty advanced thing. They were some of the first doctors that got out their offices and built this clinic for elderly people.

EB: It focused around rehab?

JK: For people who had strokes and heart attacks.

EB: Did the war influence that decision?

JK: I don't think so. The reason I was born in Alexandria, Louisiana was, that Alexandria was the closest that they'd let my father get to the front during World War II. He was at the VA at Alexandria, Louisiana. My father was an only child and my grandmother was a diabetic so my grandfather and grandmother relocated to Miami Beach and my dad wanted to be with them. So, my parents moved there and he set up his practice. I used to make house calls with my father.

EB: You made rounds with him?

JK: He used to take me on house calls. As a little kid, you can get very much into sports, so one of my dad's patients was Angelo Dundee and Angelo Dundee was a famous manager and trainer. He was Muhammad Ali's and Sugar Ray Leonard's trainer; and, he had like fifteen champions. So, whenever a fighter was in Miami and they got sick, my dad would take the house calls. So, I met all the great fighters in that era, Carmen Basilio, Sugar Ray Robinson, Rocky Marciano. I can remember just making house calls.

EB: Did that change the vision of your career, intellectually, or was it more that extracurricular?

JK: No, I just liked sports, so it was fun. You know, when my dad was raising me, we didn't have my mom around. There was an issue of where we were going to go when he went on a house call, so my sister and I would frequently go and we'd be plopped at some bar in a hotel while my dad went upstairs and examined someone. We'd be sitting at the bar; so as a consequence, my sister and I had a tremendous collection of swizzle sticks from the bars.

EB: Not doctor's tools, I would say.

JK: I used to make house calls on my tricycle when I was only four years old.

EB: Did you know you'd be a physician?

JK: I always wanted to be a doctor. I always wanted to be a physician.

EB: Why was that?

JK: I wanted to be like my dad.

EB: And, did you know what that would mean? Did you know what kind of physician you wanted to be?

- JK: I didn't have a clue; although, in retrospect, the specialty I went into was in no way an accident. Part of it had to do with, having lost my father at an early age, and he was a very popular extremely well liked competent physician. So, when I decided to go into medicine, I really did not want to have to compete with him. So I tried to do something that was different. But, as it turned out, I wound up going back to an area where we had some things in common.
- EB: Maybe we can come back to that. How about going to college? How did you decide where you'd go?
- EK: I really didn't have a clue, so I wound up going to school where my dad went. That, also, was a bit of an accident.
- EB: It was not a bad choice, though.
- JK: When I was in high school, they didn't have a lot of guidance counselors. It's not like it is now. So I remember getting this book that told you that if you were in the top ten percent of your class, these were schools you could apply to, so the University of Chicago was on that list. I said, oh, my dad went there, so I applied there and that's why I would have gone, but it was not terribly thought out. I didn't have a real good understanding of what it was going to be like to get a University of Chicago education, just somewhat different.....
- EB: Different than you expected?
- JK: I think it is somewhat different than any of the other American universities.
- EB: What did you major in?
- JK: Biochemistry..
- EB: And, why did you do that?
- JK: I think somebody told me that if I wanted to go to medical school I had to do something like that, so I was just sort of following along with what they advised me to do.
- EB: And, how did you find it? Was it intellectually stimulating for you?
- JK: I really didn't like biochemistry that much, to be honest, but I wanted to be a doctor.
- EB: And, that was the way to do it.
- JK: That seemed like the right thing to do.
- EB: And, did your idea about that particular career why you wanted to be a doctor, did that evolve in this time in your life?
- JK: Well, sort of, I wound up doing a lot of different things. I wound up getting an MD, a PhD in pharmacology and doing two residencies; so there was a bit of an odyssey, an unusual course that I wound up following.
- EB: So, you, get a PhD before you went to medical school?
- JK: Before I went to medical school, I was an undergrad at the University of Chicago and the University of Chicago is one of those unusual places

that have more graduate students than undergraduates. And, it's one of these places where research is everything and teaching is a secondary phenomenon. So, I got steeped in that tradition pretty early and I remember a guidance counselor saying to me, you know, "Kleinman, the way you're going there's no way you're going to medical school. You've got to do something to show some interest." So, I went over to the hospital and tried to get a job and an ophthalmologist said, "Well, you can come here. You know, the last guy wrote five papers and he went to Stanford Medical School". And I said, "Well, you know, sign me up". But, he didn't give me the job. By then, I decided I probably should get a job in a lab and somebody told me that somebody was looking for somebody to wash glassware in the pharmacology department. I went up to the pharmacology department to get a summer job, washing glassware, to show that I was interested.

EB: In going to medical school?

JK: Yes, and I never left that lab. That lab helped me to get into medical school and I got a PhD in that lab. And that opened some of the doors for me. I remember that summer, washing a lot of glassware. And I also learned how to do some isolated atria preps, none of which terribly interested me, but it seemed like this was going to be a good path. At the end of the summer, Hoffmann, who turned out to be one of my PhD advisors, said to me when I was a senior in college, "Would you like to do a research project with me"? I said, "Well, research is for geniuses and I didn't know if I could do it, but I'd be happy to try". So, I rearranged my senior year in college. I took biochemistry with the medical students, PCHEM with the chemistry graduate students, and I did this research project. And, then, they helped me to get into medical school.

EB: What was your research on?

JK: The metabolite of an anti-malarial agent that was being tested in Vietnam. It had nothing to do with what I was really interested in, but I wanted to learn how to do research. It didn't matter if it was in a totally unrelated area.

EB: What was it that made you want to be in the lab doing research?

JK: Because, they told me if you want to go to medical school, you have to show some interest. This was the job I was able to get that showed that I was interested, so I just took it.

EB: And, then, at some point, it felt like something that was also...

JK: It evolved into a research project. And by the time, I went to medical school and graduate school I knew that I was interested in the brain. So, I convinced my PhD advisor to let me have a second PhD advisor in neu-

ropharmacology. It was a man named, Al Heller. My two advisors were friends.

EB: Say again, what was his name?

JK: Al Heller.

EB: And, how did you get interested in the brain?

JK: That's not entirely clear. The reason that my custody was awarded to my dad was that my mom was mentally ill.

EB: And, you knew that while you were growing up?

JK: Sort of, but it wasn't entirely clear. I had sort of heard stories about it, but I didn't fully understand it.

EB: And, then, did you learn more or come to understand that while you were an undergraduate at some point?

JK: I'm trying to remember when I started to piece it all together.

EB: Maybe they weren't related. You know, some people might have a drive to cure cancer because they mother died with cancer.

JK: No, this was, not the case. I think the psychiatry thing really was something to avoid, competing with my dad. But, I did have this mentally ill mom and I can't remember when I first figured this all out. I remember going to my aunt and saying that I thought that my mom had been diagnosed with schizophrenia and my aunt then confirmed it. My mom was still alive, so I could actually talk to her about this. But, it turned out that she wasn't schizophrenic. That was a misdiagnosis.

EB: How old were you when you became aware of all this?

JK: I was probably becoming more aware of this in college and certainly in medical school.

EB: What year did you finish college?

JK: 1966.

EB: And, then, you spoke with your mother about this?

JK: I definitely talked with my mom about it. I mean, I don't think she really understood exactly why this diagnosis was made. I know people thought she was delusional. They treated her with ECT, which was not terribly useful. She wasn't really delusional. She had some bizarre ideas and probably the correct diagnosis was a really bad obsessive compulsive disorder, but not schizophrenic.

EB: Was your research, then, around schizophrenia?

JK: My first research was on this anti-malarial stuff, which, trust me, I had no interest in, whatsoever. And, the second thing was, then, that I tried to get training in neuropharmacology. And, a lot of that had to do with Heller being a very appealing mentor. And, that is what he was interested in, and Hoffman was interested in carbohydrate metabolism. So, what we

fashioned was a project to see how monoamines effected carbohydrate metabolism in brain, which was done in rats. And, that was my PhD dissertation. But, that didn't really interest me that much either, but it was good training. It was useful, because it opened up some doors for me. So, I was a medical student and I was a PhD student. They had a very fancy program at the University of Chicago in those days where they would pay for your entire medical school and PhD education. So, I was advised to apply for that, but I didn't get it, probably because I didn't have very good judgment when I filled out the financial form and when the Dean looked at it, he, basically said, no way can we give you money; you don't need money. But, I said I'm not going to do this PhD work unless somebody else pays for it. So, they paid for the PhD work and I paid for the MD work. But, the Dean also said that when I come back into medical school, they would probably pay for my last year's medical school. But the war came, and money was drying up. And, then, the NIH started a program where they would pay for your last year's medical school in return for coming to NIH to do two years of research. So, I said, well, that sounds good; I've got to get into that program. And I convinced one of the former presidents of the ACNP, Daniel X. Freedman, to write a letter for me to help me to get into the NIH. But, I got to find a lab that was willing to have me, even though I wasn't going to come for several years, because I had to finish up first medical school at the University of Chicago and do my internship and a residenc. Fortunately I got invited, after Daniel X. Freedman wrote these letters for me, to the labs of Sokoloff and Kopin, at the NIH, which were fairly prestigious labs at that time.

EB: Were they also working on monoamines?

JK: Sokoloff was interested in carbohydrate metabolism because they were going to start a PET scanning program in which they were going to use deoxyglucose.

EB: Was that very prestigious work at the time?

JK: Yes, I'm getting into that. I didn't have any knowledge of imaging. What I knew about was carbohydrate metabolism and monoamines. So, I got interviewed for that, but I wasn't the most diplomatic person in the western world. So, when Kopin was interviewing me he never looked up from lesioning a rat, and he said, you've got this PhD in Pharmacology. And, I looked at him and I said you know, I'm really not interested in working with rats anymore. So, that just killed my chances with Sokoloff and Kopin. NIH had a policy that if you weren't invited to interview, they didn't want people going all over these labs and meeting people. But I was a rule breaker. I went over to thank Lloyd Guth in the Neurology Institute who had helped me with my PhD work, and told him what happened.

I also asked him whether he would take me. He said to me, well, I do mostly rat research. If you change your mind, I'll take you in my lab, but I really didn't want to change my mind. So, I figured I'd go to another lab. And, then, I did something else that wasn't too swift; I went to Julius Axelrod's lab. But he was, as you know, a basic scientist and it was going to be more rats, but I just wanted to go in there. I went in there and I told him who I was and he threw me out of his office, you know. He told me I can't take anyone in this program and that was over in ten seconds.

EB: He knew you were too junior?

JK: No, he just didn't have an opening for a person in that program. So, I went to Fred Goodwin's office, and Fred said, oh, we just got letters about you. Could we meet for lunch? We'd like to consider you in our lab. I said, terrific. So I went to lunch with Fred Goodwin and he was telling me about what they were doing. By that time I had already really gotten hung up on this schizophrenia stuff, even though, I really hadn't done anything about it and he wasn't doing that. He was doing work with affective disorders. And, again, I wasn't too diplomatic, so I told him I was really interested in schizophrenia, not the affective disorders. So that sort of killed that possibility right off the bat. And, then, we got into a second dispute which was about psychoanalysis and I was of the opinion, not that I had any right to have any opinion at this point in my life, that people who were going to become psychiatrists should be analyzed. And, he took the opposite stance; although, ironically, he had some analytic training. So, we had this argument at lunch. And, while I was having an argument with Fred Goodwin at lunch, another investigator of the Institute, Richard Wyatt, was listening to me. He had just started his schizophrenia research at St. Elizabeths Hospital and he and Fred were somewhat competitive. So, he said, would you like to come down and interview for this position in this new lab we're forming at St. Elizabeths, which is not even on the main campus.

EB: Yes, but would it count for the NIH?

JK: Yes, this was an NIH lab that Seymour Kety and others had set up at St. Elizabeths'.

EB: Are they doing drug trials there?

JK: No, they are doing real schizophrenia research. .

EB: Real, what do you mean real?

JK: To study the disease in patients. St. Elizabeths is an insane asylum.

EB: But, weren't they doing drug trials?

JK: We did some clinical drug trials, but mostly we did research on what was causing this illness. Now, St. Elizabeths is in southeast Washington. It is an insane asylum surrounded by a slum. So, I took a cab down there and

got into the building. I went up to the fourth floor and got off the elevator. In those days, I had hair and a goatee and what not, and the elevator door opened and a patient looked at me and he yelled, "Satan". I realized I was in the right place where I wanted to be to do research.

EB: Had you done your residency at this point or was this before?

JK: This is before I had done my residency. This was my dream to do this research, at this point. I was not certain exactly why, but this is what I wanted to do.

EB: You knew before that, that you wanted to work with people, not rats.

JK: That's right and I wanted work to with sick people and I wanted to do something meaningful. So, this was my dream job and I was the first fellow that Richard Wyatt hired. I didn't come that day. People came before me, but I was the first one they ever hired, as far as I know.

EB: Do you feel like your research from that point, and your career has an overriding goal and objective?

JK: Yes, it was to get at the root of what causes schizophrenia, and that became what I did all of my research on. This is a little bit of a long-winded story, but that's how it happened.

EB: Right.

JK: So, then, I went back to the University of Chicago. They paid for my last year of medical school. I did an internship at the San Francisco General, did a residency at Mass Mental, which used to be called Boston Psychopathic at the time, and came down to Washington. I told my wife we were just coming for two years. I was supposed to go back to the University of Chicago and be on the faculty. That was our plan. At one point in my first year, Richard Wyatt turned to me and said, you know, we're collecting these brains for this post-mortem brain research and we need to recruit some people. I had a bunch of friends - I'd left a year earlier from Mass Mental - who, like Dan Weinberger, David Shilling and some others did their residency with me, and he wanted to recruit these people. So I started inviting these people down, even though, I was only a first year Fellow, to recruit them to do this post-mortem brain research. I couldn't get anybody to take this job, but I convinced myself that it was worth doing. So, I went to Richard and I said, "I really can't find anybody that will do this and I really think it's something that I want to do". He said, "Well, you can't do this, because you're only going to be here two years. If you want to do this, you have to stay for a third year". So, I asked my wife if that would be OK and she said, "OK, as long as we can go back to Chicago"; her parents were on the faculty at the University of Chicago. So, we had this agreement, but by the time I got ready to go

back the situation in Chicago didn't go exactly as was expected and the offer wasn't the best position. So, I think at that point, Daniel X. Freeman said I should stay at the NIMH. And so I did for the rest of my research career.

EB: You've been at NIH for your whole career?

JK: Yes.

EB: How long did you work on the post-mortem project?

JK: The whole time.

EB: Your whole career?

JK: Yes.

EB: So, the lab that you kind of set up, you were the one that was running it?

JK: Well, I was in Richard Wyatt's lab and those were his resources. He got me started doing that and, then, I managed to take that a step further and that's what I wound up doing. At the end of my first year, I did convince Dan Weinberger to come down, who was my buddy from my residency, and he came and he started doing the neuroimaging work. And we've been at this for the last twenty-eight years.

EB: Post-mortem and imaging.

JK: Dan did the imaging work. I did the post-mortem work.

EB: You haven't ever gotten into the imaging?

JK: Basically not; I stayed pretty much exclusively, post-mortem.

EB: Why did you think that this will work for you?

JK: Well, I am convinced that schizophrenia was a brain disease and if you want to study a brain disease, you need brains. You can study live people, but in live people there are limitations on what you can measure. If you want to measure and get the cellular molecular basis of the illness, you need brains.

EB: And to do this work you were to become a neurologist.

JK: For neurologists it was a good idea what I was doing whereas for psychiatrists it wasn't necessarily such a good idea. As a matter of fact, one of my mentors, a psychiatrist, who is a member of this society, told me at the time that he thought it wasn't such a good idea.

EB: He thought you wouldn't find anything?

JK: Right. He was trying to recruit me to come to the University of Chicago. When he heard what I was doing, he said, you know, that's probably not the most useful thing to do. But I was already pretty convinced that it was, so I sort of stuck to my guns.

EB: Did he think that the causes of schizophrenia were environmental?

JK: No, I think he thought they were biological. There are a lot of problems doing post-mortem studies. You're not getting brains as fast you'd like, and there are many confounds that were challenging to get this work

done properly. So, it's taken a long time to make this project as useful as I thought it could be.

EB: Wherefrom did you get the funding for your research at the time?

JK: Well, the funding, when I first came as a Fellow, was Richard's funding and that was very secure. Then, I won tenure and, basically, had secure-funding.

EB: Have you had non-federal sources of funding, as well?

JK: Very little. Occasionally we get a grant from outside, but we're part of the NIH intramural research program so we're funded by the federal government. We get reviewed every four years and we have to do well on review. If we don't do well, they cut your budget.

EB: In general, it's gone well for you?

JK: I've had pretty good reviews over the years.

EB: How would you describe your lab management style?

JK: I'm interested in being successful, and I am aware that every person is different. Some people need to be pushed and some people need to be pulled. And, you know, you have to use all your skills to get people to work together, because such a project can't be done by one individual or even by several individuals from the same discipline. When you do post-mortem research in schizophrenia you need to have a neuropathologist, you need to have a neuroanatomist, you need to have a neurobiologist, and you need to have a psychiatrist. So, my job was to get these people to work together and make this thing go.

EB: So, what would you say, as the Head of the lab, your greatest strength was?

JK: I made it go.

EB: Getting people work together?

JK: The only thing that matters for us is discovering something. If we can discover something, the discovery is the measure of what we do. That's what science is about and we've been very fortunate.

EB: Could you say just a couple of things that came out from your research?

JK: I think that doing post-mortem research was a smart thing to do; this was an under-investigated area, so that was sort of useful. It's probably better for other people to judge what our biggest successes were, but I think one of our biggest contribution will probably be, the discovery with Danny Weinberger's 'leadership, a number of susceptibility genes that increase the risk of schizophrenia. So, I hope that will be our biggest contribution when it's all done. One of my other mentors at the University of Chicago was an analyst, named Bruno Bettelheim and he used to look at me and said "that the surest way to make a fool out of yourself is by attempting

to predict the future". So, we can't really know for certain, but our findings so far put us in the lead in this area of research.

EB: Had you done genetic research before?

JK: Not really. One of the nice things about the NIH is that we can go off in different directions with our funds. When we change directions, we have the potential to retrain ourselves and to learn a new discipline. So, that's what we've tried to do.

EB: And, how long has that work been going on?

JK: Well, I've done the post-mortem research since 1977.

EB: And the genetic research?

JK: About ten years ago we got reviewed and one of the reviewers said that our group was doing a lot of different things, and to this Danny said, "Well, one thing we're not doing is genetics". After that review we immediately had a retreat and decided to do genetics.

EB: That was, maybe, about the time when we recognized, there wasn't going to be one schizophrenia gene, but several.

JK: I don't know if I recognized that at the time. What happened was, that in my strange odyssey of training I felt that I didn't know enough neuroanatomy, and since I couldn't go back and get another PhD in neuroanatomy, I went back and did a residency in Neurology, so I could learn neuroanatomy that would be clinically relevant. So, when I was starting my Neurology residency, the director of residency training said to me, "you will be responsible for this, you will be responsible for that, and so forth". And, the last thing she said to me was, "Oh, you will be responsible also for the rehab unit". All of a sudden I realized that what I was about to do was take care of the same type patients that my dad had and I was ready for this at this point in my life. I wasn't going to shy away from this competition. So, I did the Neurology residency. As I was going through this Neurology residency, I encountered another guy named, Bob Lauren. He is an outstanding neurologist at the Washington Hospital Center, part of the GW University residency training program. And, Lauren would have us read different articles. So the article I chose to read and present on was this discovery of the Huntington's disease gene on chromosome 4. At that point in time I became very much aware that molecular biology and genetics was about to make a staggering impact on research. And it was something that we needed to get tooled up to do in our lab.

EB: What year was it that you went back to do your Neurology residency?

JK: I finished that residency in 1985, so I probably read that paper in '84. I went back to the lab and I told Richard that we should start genetic research, but he said, "Well, we should do this, but we're probably not quite ready".

EB: So, you started about ten years later.

JK: Yes, and as the code was broken on the human genome, post-mortem human brain studies became applicable to genetic research, because we were able to measure and detect the presence of the messenger for any of the genes in post-mortem human brain, and we could genotype people. And that became the focus of our research. That's where we're at right now.

EB: And, that's where you're going?

JK: Now, we know that it's not one gene. It is multiple genes. What we're trying to do now is trying to figure out how these genes interact because we need to determine where these genes intersect to find targets for treatment. And, that's why these brains are probably pretty important.

EB: So, deciding to look at post-mortem brains was a very good thing to do.

JK: Yes, that was a crucial thing for me. And now we have the brains and we have measured all sorts of things in those brains for years. For years we never really knew what those things meant. Now, we know that we are on the right targets and we can interpret what we're finding. Identifying those susceptibility genes really changed our perspective. And, the other big thing for us was finding the allelic variations of the susceptibility genes in the normal population. You and I and everyone is carrying these allelic variations. So, you can study the allelic variations to some degree in normal human brain, and that is really important because when you study it in the brains of people that are mentally ill, you have enormous numbers of confounds from treatment to illicit drug use.

EB: So, you have done work also with normal brains?

JK: We have and it gave us a whole new window; it helped us deal with some confounds in post-mortem brain research.

EB: What other work have you done in normal brains?

JK: We've always had to have normal control brains in our studies. Then we were also trying to see in normal brains how the expression of genes changes in regions of the brains that are relevant to mental illness over the normal life span. This should give us some clues why certain psychiatric and brain illnesses begin at a certain age.

EB: That's very interesting.

JK: Did I lose you on that?

EB: No, it's very interesting.

JK: I think, perhaps, even more interesting is to see how the allelic variations and susceptibility genes affect the expression across the life span. That's what we're going to try to do in the next year.

EB: Where do your ideas come from?

JK: I borrow them from wherever I can. I'm not proud.

- EB: From the people you work with?
- JK: There are lots of bright people around me.
- EB: People with creativity.
- JK: I'm not certain, even, what creativity is, but I think we can recognize good ideas.
- EB: How important has technology been in your work, technological innovation, how has that moved you forward?
- JK: I think, for instance, the breaking of the genetic code has been a staggering advance for us, because until then, we couldn't have measured these different messenger RNAs. Now, we can take the sequence of any gene we want, construct a complement to the sequence with a riboprobe by putting a radioactive label on it, and measure the expression of this gene in the test tube or on a slide. And, if you do it on a slide you can see what type of cells they're in, what layers they are in, you can measure the amount. These are things that you couldn't do before.
- EB: Do you own any patents?
- JK: Zero.
- EB: You're not allowed to?
- JK: I am.
- EB: Oh, you are.
- JK: Yes.
- EB: Is there a reason you don't?
- JK: I just never did anything worth patenting, as far as I can tell.
- EB: I have a few questions about ethical considerations about the work that you do.
- JK: Go for it.
- EB: Though science can do many things, it cannot decide what it ought to do; it cannot supply us with an ethic. Humans do this. Are there things that you decide that you ought not to do for ethical considerations?
- JK: Geez. You know, we can't do anything that isn't approved by an IRB official review board. So, we have guidance from that. I usually think I know what's right or wrong, so I would not want to do anything that I thought was wrong or unethical; although, I recognize that not everybody will agree on what's ethical or not. I don't know if that answers your question.
- EB: It does. Do you find the IRB process helpful?
- JK: Everybody thinks they know what's right, and the IRB process makes it certain that there's some general agreement on what you're doing is ethical and right. That's one of the functions of the IRB.
- EB: Have you had any instances in your career in which you were surprised by some concerns raised by an IRB.

JK: I'm always surprised what comes up in the IRB, but for myself, I'm not aware of being involved in any great ethical controversies.

EB: Has your work raised some ethical questions?

JK: I'm certain it did, but I don't think that any ethical question has been raised about me, at least, I hope not.

EB: And, for others, who do work like you, in what way have ethical concerns been made?

JK: I really don't think I'm going to be able to answer that one. I'm sorry. I don't mean to be secretive, but there are some other investigators that this has been an issue for, and I don't really think it would be appropriate for me to comment on them.

EB: So, we can leave it at that.

JK: You can ask me in terms of post-mortem human brain research, the research that I do. You know, we've tried to comply with all the regulations that we've been asked to do and I think the other people have too.

EB: You've had an interesting career, having worked at the NIH throughout. Do you have any thoughts or concerns about the rise of privatized science or industry around your area of interest?

JK: I'm not really concerned about that. My attitude is that many contributions have been made in both, the public sector and the private sector. If people make money at it, I have no objection to that. We wouldn't have any drugs for psychiatric patients if the pharmaceutical companies weren't making money. I think they make enormous contributions. On the other hand, some of the research we do at the NIH probably could not be supported very readily by a private company, because we don't have a product within the usual reach in time what an investor would be willing to wait for. It may be ten years before the kind of research we do will have any tangible result.

EB: So, it hasn't happened in your lab that you've gotten close to something that a company might be interested in?

JK: There was a period where the biotech world was very interested in intellectual property, but I think that's not any longer what it used to be. Since we did not have deliverables, the bubble around biotech burst, because companies want deliverables. So, somebody has to fund the research that maybe five years away from producing deliverables. The reason I don't have any patent is that we don't have any deliverables.

EB: Were you involved in anything that was of biotech interest?

JK: I actually had a NIH approved outside activity in a company to discover things. But, as the bubble burst, the company disappeared. That's the way it goes.

EB: What was that like?

- JK: It was great. I learned a lot. And, that was the key to it, actually. The federal government has put all sorts of restrictions on what we can do in terms of conflict of interest, but what I learned at that biotech company I've brought back to the federal government. They've profited from it in developing research.
- EB: What for example did you learn?
- JK: The approach of how to use genes to study brains; I didn't learn that in the NIH. I learned that working in this company. So, that, I think, was very useful.
- EB: Can you be more specific?
- JK: We were interested in eating disorders, in finding genes, relevant to eating disorders. This was not something my lab at NIH was interested in. So, to me, it's somewhat regrettable that some of these new regulations have come into place that may not further the collaborations between the private industries and the federal government. As a matter of fact, some of the new regulations that have been proposed, in my personal opinion, led to the burst of the bubble of biotech companies.
- EB: What led to the burst of the bubble?
- JK: A lot of companies sprung up to patent genes they discovered. The day that Clinton made that announcement that they couldn't patent genes, the bubble burst, I don't think the biotech work will ever recover. I don't think you could get people any longer funding a company that was just going to discover genes.
- EB: What about diagnostic probes that might have a clinical life?
- JK: Since all the genes of single gene illnesses, those low hanging fruits, are gone, everything that is left are complex genetic disorders, multiple genes of small effect interacting with environmental factors. So, getting a test out of that may yet happen, but it isn't going to be easy. So, if you were going to invest in that, I would not advise you to.
- EB: I want to know a little about the people that work with you, in terms of their gender breakdown. Do you have women in your lab?
- JK: I have a lot of women in the lab.
- EB: And, how about foreign people?
- JK: Tons of foreign people, tons of women. That's not something that I should really take pride in. We take people from every part of the planet, I don't care if they have three heads or they're purple, or if they're hermaphrodites, we're just looking for good scientists to discover something. That's really what we're supposed to do.
- EB: Do you think women do science differently?
- JK: Do it differently? No, I don't really think that. Maybe, I'm missing the point of the question.

EB: No.

JK: The idea in science is to discover something. Women are just as capable of discovering something as men, possibly more so, for all that I know.. .

EB: Why is it that you have a lot of women in the lab?

JK: I have no idea, but my neuropathologist is a woman. The major molecular biologist in my lab is a woman. The only tenure track person in my lab is a woman, so we have lots of female Fellows. I think we have more female Fellows than male Fellows.

EB: Do you think you're doing something right or is that just coincidental?

JK: My attitude is to hire the best people I can and I tried not to pick people on the basis of gender. I think that would be unethical and it would be a violation of Federal laws. I wouldn't do that.

EB: Well, I mean, you talked about building a team, getting a team motivated to succeed and, maybe...

JK: We have a lot of fights in this group, but I don't know if that has anything to do with people's gender.

EB: Do you think there are things that need to be done to increase the number of people in science? Do you worry about that?

JK: I think we've got a big problem coming down the road related to education, and especially, physician's education in the United States. Most people are saddled with such debts in medical school that it becomes very difficult for them to go into research and the NIH. When I applied for my job way back when I was in medical school or when I was hiring people when I first got to NIH, we were getting twenty applicants for every position. We're lucky if we have twenty people apply for the entire NIMH program at this point. So, I think it's a huge problem.

EB: Do you think this has to do with finances?

JK: I think that's part of it. I think the federal government doesn't subsidize medical education as much as they used to; although, I don't have those facts right in front of me. Maybe, the research will all be taken over by PhD's. I think the problem with that is that NIH, the NIMH, is supposed to study illnesses and it would probably be useful to make certain that you have some people that really understand illnesses.

EB: Do you still do clinical work?

JK: I had a private practice, approved by the NIH for outside moonlighting, for many years, but I stopped it a few years ago, because there were just too many things to do. But, I still see patients on the side.

EB: You treat people with schizophrenia?

JK: Oh, yes. I saw them in my house. My daughters were my receptionists. I made house calls, as of not too long ago.

EB: And, it helped your research, do you think?

JK: I think it kept it grounded and made certain that my hypotheses were focused on these patients.

EB: What's the best part about your job?

JK: Every day when I go to work, we're discovering something. You know, the pace of discovery in the lab is staggering right now. It's rare that a week or two weeks goes by that we don't find something interesting. I work with a lot of bright interesting people. The job is never boring. And, as a physician, having an opportunity to do research to help patients, I think, it is a wonderful opportunity; I'd do the same thing all over again. It's just a really great career. It's been fun. I was paid well. It's just been great.

EB: What's the worst part of it?

JK: I couldn't think of what the worst part of it is. I remember, though, when I was a boy, my dad, gave me *Microbe Hunters* to read. I don't know if you're familiar with that. It's about Pasteur, Madame Curry...

EB: Oh, *Microbe Hunters*?

JK: Yes. And, I think even I would never be able to compare myself with those great people, the fact that I have been able to do work like that is a wonderful opportunity.

EB: Is there anything that you think we should have talked about, that we missed?

JK: No.

EB: Good.

JK: You got what you wanted?

EB: Absolutely.

JK: All right. I may never have the courage to look at this.

EB: That was great.

JK: I think, oh, geez, what's my sister going to say when she reads this?

STEPHEN H. KOSLOW

**Interviewed by Thomas A. Ban
Acapulco, Mexico, December 15, 1999**

TB: We are at the 38th Annual Meeting of the American College of Neuropsychopharmacology in Acapulco, Mexico. It is December 15, 1999. I will be interviewing Dr. Stephen H. Koslow* for the American College of Neuropsychopharmacology. I am Thomas Ban. Could you tell us where you were born, brought up and something about your early interests and education?

SK: I was born in New York City, spending all of my childhood years there going to school. I went to college at Columbia University. After I graduated I left New York for the first time and went to Chicago. What brought me to Chicago was the University of Chicago. I was enrolled in the Department of Pharmacology to study psychopharmacology, get a Ph.D. degree and pursue the area of brain research. This is an area that has always interested me and I thought it was the most challenging in terms of all scientific areas.

TB: Who was the Chairman of Pharmacology at the time?

SK: The Chair was Lloyd Roth and he was also my PhD mentor. He was interested in using radioactive tracers to look at distributions of drugs in the brain and he developed some very sophisticated autoradiographic methods. He had done whole body radiography and then he developed a cellular method for autoradiography, so he could look at where the drugs localized at the cellular sites. He was a great mentor; and the department focused on the central nervous system and neuropharmacology. To my knowledge, in those days there was not much around in terms of neuropharmacology. There were few texts to speak of. It was really the beginning of the modern era of brain research and the University of Chicago had some great scientists who showed us, and taught us how to think about how the brain might operate and gave us a good chance to get into the field of brain research.

TB: Could you tell us about brain research in those days? Am I correct that we are in the early 1960s?

SK: I was at the University of Chicago from 1962 through 1967. In those days, brain research was really a black box, no matter where you studied; even if you were in laboratories looking at how drugs worked. At that time, we had, what probably looks now to be a trivial argument, whether serotonin, norepinephrine, and dopamine were neurotransmitters and whether they

* Stephen H. Koslow was born in New York City, New York in 1940.

really existed in the nerves and functioned as neurotransmitters. These are the things I grew up on; learning about how the brain worked. We thought at that time that we had a great deal of knowledge and understanding in terms of brain mechanisms and how drugs worked in the brain.

TB: What was your dissertation on?

SK: My dissertation dealt with anticonvulsant drugs and their site of action in the brain. This was my real first research experience. This research led me to believe that it was important to study drug mechanism of action at the cellular level. After I finished my degree at the University in 1967, I had a post-doctoral fellowship in Sweden. What I wanted to do was to look at how drugs worked at the cellular level. There was a researcher at the Karolinska Institute, Dr. Enzo Giacobini, who was studying single cells from the nervous system. He was isolating them, and studying how they functioned biochemically. He agreed that I could come and study how anticonvulsant drugs acted at the cellular level. Well, no surprise it was not really possible to do the specific study that I wanted to do but going to the Karolinska Institute for a couple of years was a very rich experience. It was really great to have the exposure to the Swedish community and in particular the Karolinska scientific community and to the variety of brain research that was being done there.

TB: Could you tell us about what you learned?

SK: I learned how to isolate single cells and look at microchemistry of cells. And I also became interested in neuronal regeneration. We did some interesting regeneration experiments in the peripheral nervous system, reconnecting different nerves to each other and looking at their function and chemistry. Many of the people that I worked with there made it a very rewarding rich experience.

TB: With whom did you work?

SK: My post doctoral sponsor was Dr. Enzo Giacobini. Among those I interacted with at the Karolinska Institute were Thomas Hoekfelt, and Lars Olsen and Urban Ungerstadt. It was an outstanding opportunity to interact with people making important contributions to the understanding of brain function, to understanding the morphology, cellular connections and chemistry of the brain. The big question was what to do when I returned to the US. I was interviewed by Mimo Costa, who headed a key research group in the Intramural Research Program of NIMH at Saint Elizabeths Hospital. He was just developing a big research program there and he offered me the possibility to come back as a Fellow and work with him. He liked some of the things we were doing in regeneration. He also believed that it was important to do studies at the cellular level. On

returning to the US I came back to Dr. Costa's group at Saint Elizabeths' Hospital in Washington, DC. On the personal side, while in Sweden we had our first child, a daughter. We came back to the United States with a Swedish baby, so to speak, and settled in Maryland to allow me to work at Saint Elizabeths for a number of years.

TB: Could you tell us about the research you did at Saint Elizabeths'?

SK: I continued to do research on regeneration. Dr. Costa asked me to develop chemical methods for looking at small quantities of messenger RNA. He asked me to do this because he felt it was very important to have this capability to extend his research which at the time was focused on neuronal neurotransmitter turnover rate. At that time, there were no methods to look at small quantities of mRNA. The research went exceedingly slow. There was also a chemist in the laboratory, looking at gas chromatographic mass spectrometric methods to do the same thing. Dr. Costa suggested that we work together and try to develop quantitative methods for measuring extremely small quantities/concentrations of neurotransmitters. Within a short period of time Flaminio Cattabenni and I managed to develop a very sensitive quantitative method to look at the major neurotransmitters, which, at the time were serotonin, norepinephrine, and dopamine and their metabolites. We proceeded to develop this method and did some interesting studies to demonstrate where neurotransmitters were in the brain even if not quite at a cellular level, but close to cellular level. We used a new term to define our quantitative sensitivity. This was femtomole, reflecting the low concentrations we were able to measure. That was a busy period in my life. My wife was going back to school to get a degree in psychology; we had our second child, and, as you know, when you work in a lab you spend many hours there. It was an extremely productive period developing new methods and approaches to study the brain. But, I felt at that time, that I was getting narrow in my pursuit and needed to stand back to be able to look at theoretical issues. To overcome this deficiency I accepted a position in the extramural research program at NIMH. The position was in the clinical research branch. The Head of the branch was Dr. Martin Katz, who is also a member of the ACNP.

TB: What was your assignment in the clinical research branch?

SK: I was responsible for making decisions about funding and stimulating the development of research in the field of biological psychiatry. The branch I worked funded biological approaches to clinical problems, and I had responsibility for the basic research focus in the branch. This was fascinating because it gave me an opportunity to learn about the clinical side of mental illnesses and meet with some of the outstanding research leaders of that day and get some insight into what their research and

problems were about. This was a real growth period in terms of expanding my horizons about how the brain worked, and also how clinicians looked at the brain and thought about understanding mental disorders. During that period, Dr. Martin Katz was working with Drs. James Maas and John Davis and others to develop a multicenter study to look at experimental approaches to study the biology of depression. At that time, all of the theories of depression were derived from small studies in which biogenic amines were a central theme. In those studies the biogenic amines may not have been measured with the greatest accuracy and the diagnostic procedures were different from one study to another. There were many neurochemical theories of depression. Marty, Jim and John designed a study that would test these hypotheses in a large population of individuals using a new standardized diagnostic system across all of the research sites. They brought together scientists who had expertise in endocrinology, biochemistry, and clinical diagnosis and designed an in hospital study with depressed patient along with a normal control group. The study started with a washout period for both patients and controls. Patients and controls were evaluated using the same protocol and the patients were re-evaluated after pharmacotherapy by measuring biochemical and behavioral changes. It wasn't an experimental study to develop new drugs, but rather it was testing the effects of existing effective drugs. We used tricyclic antidepressants and studied behavior, and biochemical measures in cerebrospinal fluid and urine, as well as endocrine changes. It was a fantastic experience to be responsible for coordinating this study. We did the study over a five year period. We had 150 depressed subjects who were treated and about 80 normal healthy controls. Both groups went through the same baseline procedures. The findings were interesting but I guess, disappointing.

TB: Why were the findings disappointing?

SK: Because, they didn't support the major existing hypotheses, but rather added to the controversy. While it was clear there were disturbances, based on the measures taken, they were not as major as people thought they would be and it remained unclear what the exact alterations are in the disease. We really couldn't support any of the biochemical hypotheses, creating chaos in our thinking and in the thinking of others. Another major controversy arising from this study was whether it takes two to three weeks for the drug to start to work as suggested on the basis of other clinical and basic neuropharmacological research. The behavioral findings are based, for example, on Hamilton Depression Rating Scale scores, a very global measure of symptoms in depression and not on fine measures of behavior. In our study, we looked the Hamilton scores as

well as more refined measures of behavior and we saw that early on, soon after treatment began, patients started to change in terms of their anxiety ratings and other symptoms, all decreasing in intensity, before changes were noted in the more global Hamilton scores. I think this is a major issue that needs to be researched more carefully. There is a need to include more refined behavioral measures in clinical studies to be able to look at the behavioral components of the disorders, not just the global clinical measures of depression. Unfortunately, when we designed the study, we used the published literature as our guide and looked for changes that could take place after two weeks of drug therapy. All the biochemical measures were taken at baseline and then two weeks after drug therapy. Luckily, we had behavioral measures on a daily basis. So, we could see from the behavioral measures that the changes started pretty much soon after drug treatment initiation. Marty is following up this issue to answer the question whether the drugs start the recovery process early on, as we believe the data demonstrated in our in study.

TB: Would it then be correct to say that your data did not support biochemical theories of depression and about the mode of action of antidepressants? Would it be correct to say that your data showed detectable treatment effects without a two to three weeks delay, shortly after commencement of treatment?

SK: That is true. The study was very rewarding in terms what we learned from it. We published our findings and the ACNP provided an excellent forum for discussing with other scientists about what our findings meant. At the time that study was conducted I still had other responsibilities of stimulating and funding grants in biological psychiatry at the Institute. But while coordinating the study I was also able to return to my major interest: how basic brain functions operate.

TB: Are we in the late 1970s?

SK: This is now around the early 1980s and by that time it was clear to me, a basic neuroscientist, that the NIMH should invest more money in basic neuroscience. I convinced the institute leadership to think about creating an extramural program for funding neuroscience and a Neuroscience Research Branch. They did create it in 1983, and I became the first branch chief. I proceeded to develop a program in Neuroscience to look at basic brain mechanisms in order to better understand the functional pathology of mental disorders. This program developed quite nicely over the next seven years. Each year there were more neuroscientists and more questions to be answered. It was a great experience and opportunity to develop this program. In the 1980s, the molecular biology revolution was beginning. We tried to introduce people into this area of research. It was

very stimulating and rewarding to see people start to move in the new directions using molecular approaches. I think the program did extremely well; one could see the field changing. It was also reflected in the ACNP which became much neuroscience oriented, and less clinical, to the unhappiness of some members and the happiness of some others.

TB: So, you think that the implementation of your program played a role in the move from clinical research to neuroscience in ACNP meetings.

SK: I think there was a group of us that wanted to see psychiatry based on biology. Initially, I thought it was a good meeting because I could learn about the clinical aspects of brain research and disorders, but I wanted to see more information on how the brain actually works transmitted to clinicians. During this period, I also promoted efforts at the NIMH to support research on imaging. Imaging offers a unique window on the brain; that could allow us to do innovative studies. I think by now, everyone understands that imaging is a powerful tool for understanding the brain in health and disease. We are still struggling with the methodology of imaging because however powerful, it still has limitations. Now, there are multiple ways to image the brain that are more powerful than what we had in the '80s, which was limited at that time to positron emission tomography. When Lew Judd became Director of the Institute, he was interested in seeing neuroscience applications in psychiatry grow even more rapidly. He created a Division of Neuroscience and I was appointed as the Director of this new division. Given this opportunity we developed many more research programs. There was greater investment in supporting research on understanding the brain from the point of view of molecular mechanisms. This was exciting. It was also the beginning of the Decade of the Brain; a marvelous period of pursuing knowledge about how the brain works. There were an increasing number of people interested in pursuing brain research. There are currently about 30,000 people, who attend neuroscience meetings annually in the United States.. If you think about the type and amount of data that is generated by all these people, it is enormously rich. I'm saying this because this is really where my focus is now at the Institute; trying to stimulate the field to do research in specific new areas. The issue, basically is, that at this point in time with all of the advances in technology and approaches to study brain function, we have a richness of data that isn't totally utilized by everyone, even by the researchers who have created the data. Most people will do experiments to answer a specific question and once they answer that question and publish the paper, the data is usually put on a shelf someplace and never looked at again. But, if one wanted to reanalyze the data or ask slightly different questions,

you could do that if the data was available. The way we do research today, they are not available. I believe that we are in the middle of a very exciting new revolution.

TB: What revolution are you referring to?

SK: The information technology revolution. We are all impacted by it in every way and state of our lives. We need to take advantage of the new technology and do something different in the way we do science; we need to have a paradigm shift in how science is carried out and allow our data to be shared more universally; and allow our data to be mined by other scientists. It is not only the amount of data that creates this need, but also the way neuroscience and brain research is done today. Because of the complexity of the brain and the highly specialized technology used it is very difficult to study the brain as an intact organ. This doesn't allow you to look across levels of function, across levels of analysis. Look at the journals that are published in neuroscience research today. There are some very broad journals like *Brain Research*, and *Journal of Neuroscience*, and then there are journals restricted to the synapse, hippocampus, etc. This specialization has led to fractionation of the data. As a field we need to try to rebuild the brain from all of the fractionated data that we have in order to understand how the brain works because this fractionated approach is not going to have as quick of a payoff as if we were able to put all of the data back together again and look at it in term of systems and whole brain function. We are collecting data at an extremely rapid rate; there are 200 brain research journals published each month. Anyone who writes a grant application or a paper needs to spend days, if not weeks, in the library trying to recover data from the literature. If we were using modern IT we could hit a button to have all of that data come to your PC, and that would be fantastic and liberating. To be able to manipulate and re-analyze original raw data would be even better. To accomplish this, the NIMH started a program in 1993 called "The Human Brain" project; we now also call it Neuroinformatics.

TB: What is the objective of the new program?

SK: The goal of this program is to set up databases that would be on a distributed system and be accessible via the Web using search browsers that can pull data into your computer and, then, you can create your own unique database to query specific questions of the data. This would be similar to what has occurred in genomics, where bioinformatics has led to the creation of national databases of the human genome and other genomes from different species. But, for all the data that exists in neuroscience, it would be too large of a database to try and centralize it. We currently believe that the best approach is to set up a system of

distributed` databases where each investigator or group of investigators can get together and create a database for each data types they are working on in their own data model. Since everyone likely has their individual model, in across data models, there would be overlapping areas that could be used to fuse data across levels of analysis and to combine data to look at how brain function might be integrated. Another important aspect is the understanding of the complexity of the brain. We have to be able to construct theoretical mathematical models. We have seen models developed for ion channels of individual neurons. There are now unique mathematical model platforms which allow one to plug in different experimental values to explore nerve cell function under different conditions. By using theoretical mathematical models, we can go back and forth between experiments and theory and push experiments further through queries of the model. From what you learn in this approach, you go back and change the model. It is an iterative process of building a greater understanding of how systems work. We need to have models from single neuron levels, from the gene level up through the systems level, and ultimately the whole brain in order truly understand the brain. This approach should help put the different pieces back together again. At this point, I find this one of the most exciting challenges and opportunities for the field of science. I think people are slowly starting to agree that this is important to do, but many people are resistant because they worry about sharing data.

TB: Sharing data is a sensitive issue?

SK: A frequent question I get when I talk about this program is: you mean you want someone else to look at my data? And, I say, yes, that is true. Scientists are concerned that others will find out a different answer by looking at the same data that may be true. The reality is that, if someone can reanalyze someone else's data and come up with a different possible answer that may move us forward. For this to happen would require a paradigm shift in both the way individuals think about someone else looking at their data and also about the way we reward the scientific endeavor. Currently, scientists are evaluated and rewarded for journal publications. I don't believe this should change. When we think about sharing data, we agree that individuals should publish their data first and then share their data, and not share it before they publish it. The scientific vetting through peer review is critical prior to data sharing. If this sharing of data works, then, we also have to give rewards for people who create databases and contribute to databases, to people who create some of the algorithms for models and not just for publishing scientific results. This can be a stumbling block because it has to be built into the system,

both at the university level in terms of promotion, and also in the grant review mechanism when evaluating a person's career. I find this a most exciting and challenging opportunity.

TB: Did you ever return to laboratory research?

SK: I never went back to lab research but instead stayed with the NIMH extramural programs. I made this decision because it is a unique opportunity to contribute to science in a way that you could not do in the lab. It is very stimulating to try and see what new opportunities are there and how the field can best use them to move forward in brain exploration. It has been rewarding to see that what you think is right and suggest to the field, that they embrace it. It doesn't always happen, but most of the time it does and it's great to see the field move forward. I didn't have the need to go back and work at a bench to feel that I was scientifically involved, invested and making a significant contribution in advancing the field of brain research. I felt it was very important for our field to have a representative voice within the NIMH. It was a rich experience to be able to do this. It has been great fun, extremely rewarding to see the field moving; the frustration is the slowness with which it moves. If I look back at my career at the Institute I was trying to push imaging in the early 1980s and remember a lot of starts and false starts, and now it is a major research focus and everyone wants to do it. It has produced great new insights into brain function and mental illnesses.

TB: During the past 30 years or so you collaborated with many people. Would you like to mention by name a few?

SK: I have been fortunate and honored to have the opportunity to work and interact with many great scientists and leading researchers. I already mentioned my mentor at the University of Chicago and Marty Katz; and NIMH who taught me a lot. But, also working with Mimo Costa was a marvelous experience. He is a great scientist and intellectually engaging. He is a very warm person who taught me a lot about how to think about how the brain works and how to design critical experiments to answer questions. It was a great shaping effect about the way I think about the brain. So, he was terrific. In the collaborative program I established great working relationships and friendship with some of the outstanding scientists in psychiatric research like Jim Maas, Peter Stokes, John Davis, and a whole bunch of people who are now mainstream researchers, like Charlie Bowden, Regina Casper, Alan Frazer and Jim Kocsis. The ACNP has given me the opportunity to meet a lot of top researchers in the field and to learn from them and to take what I've learned from them and apply it to my job to try and help move the field forward. It has been a great opportunity to work at the Institute and to have the opportunity to

impact on the field in a unique way. From my perspective it's been just as enriching as working in a laboratory and pursuing your own interests and understanding how the brain works.

TB: Are you pleased with the progress you are making in your program?

SK: It is progressing at a reasonable rate. In the United States we have about 20 grants that are funded to create databases and the needed electronic tools for data sharing. These activities are forming the nexus for neuroinformatics. To make this work, it has to occur globally, because research is done around the world. We have established a working group with the European Commission of the European Union. They are now funding, in Europe, similar types of neuroinformatics research and we coordinate their research with the research done in this country. They now have funded, for example, one consortium of workers who are creating a database on the cerebral cortex. This will be a fascinating database that will integrate the data from the different areas of research related to the cerebral cortex including connectivity, electrophysiology, pathology, etc. I've also been working with a working group at the OECD. As you probably know the OECD was established in Paris after World War II to help Europe recover economically from the war. In the 1990s, they started the Mega Science Forum that organized meetings around common scientific problems and provided recommendations on their resolution. Most of the discussions dealt at the beginning with the field of physics, but in '95 they expanded to include other fields. At that time the US proposed a working group in neuroinformatics. It was accepted and we have worked with other countries around the globe to start programs in Neuroinformatics. This program is taking on its own life and it is exciting to see that it is happening globally.

TB: So, by now I assume there are databases being created in many areas?

SK: Yes, we have a number of grants now that are funded to create databases for imaging, electrophysiological data, neurotransmitters and receptor systems and so on. In the next month, I have an organizational meeting with about 50 scientists to discuss central organizational issues in neuroinformatics and how to organize a grant submission to establish an International database on cognitive function. At this meeting, we will also be discussing how to organize similar efforts along all the clinical science and research areas..

TB: How long have you been in your current position?

SK: I now have a new position at the Institute, which is Associate Director and Head of the Office of Neuroinformatics, because this is the area where I want to focus and concentrate on.

- TB: Could we switch to your involvement with ACNP? When did you become a member?
- SK: I have been a member of the ACNP since 1976 or 1977. This has been one of my favorite organizations. I have served on many ACNP committees.
- TB: On which committees did you serve?
- SK: I chaired for one year the program committee and I served also on the credentials committee. And Marty and I, in the late 1970s and '80s convinced the ACNP to start its own journal. It is rewarding to see that the Journal now has its own life and is doing well.
- TB: So, it was you and Marty who suggested that ACNP should have a journal?
- SK: Yes, we suggested and talked to a lot of people to help make it happen.
- TB: Would you like to mention some other organizations you have been involved with?
- SK: I participate in Neuroscience but not to the same degree.
- TB: Are you involved with any of the neuroscience journals?
- SK: I sit on a number of editorial boards. I was on the editorial board of the ACNP journal at the beginning and now serve on the board of an imaging and a pharmacology journal. There are a couple of computer journal editorial boards I also serve on. It is always fun. But, it is hard to see what kind of impact you have on those journals.
- TB: What would you consider as your most important responsibility in your job?
- SK: My philosophy in working in the federal government is that it's our job to look to the future and ensure that the resources are there for scientists to do their work. It is my responsibility to make things happen to generate new interests and exposures.
- TB: What would you like to see happen in the future?
- SK: There are a couple of things that I would like to see happen. I would like to see more groups get together to create databases focused on specific areas. We could take any of the sessions here and in each there is a group of investigators who could work together to create a database. One of the problems in doing this is that we have the scientific expertise, but we don't have the expertise on informatics. This will require scientists to establish relationships with informatics scientists to make it work, to build the right types of databases. Most of the databases that we have today are built for financial and business communities, and our data doesn't easily fit into those types of databases. It is going to take extra work to find a computer scientist to work with to create the database. I believe that it is extremely important to have a database for every class of drugs. Would we have that we would have all of the basic data used

in publication in one place and you could retrieve it, re-analyze it from your own perspective. When you start to think of the elements of such a database, it gets huge. I think you have to start with many small unique databases that you can draw from. There was a session yesterday at this meeting, for example, that dealt with the anatomy, connectivity, and the function of different circuitries in normal brains and in disease states. It would be a wonderful database to have all of that information available in a searchable database. There is not one and we have to create it. To do that, we have developed a unique mechanism to support database creation. We also are offering grant support for people to create courses in Neuroinformatics and to provide training in Neuroinformatics as well as career awards in Neuroinformatics to support scientists in their post-doctoral years to get training in Neuroinformatics. We should also help to develop scientists who are not neuroscientists or information scientists but Neuroinformatics researchers. They would have cross training in computer and neuroscience. What I see as the ultimate goal is that you turn on your PC at home or in the office and by pointing and clicking on brain areas you can get whatever type of information you want ranging from genes to behavior and then you can zoom in on that information, and can fit your own data to it. You could examine the data in any way you would like, but, that is down the road, we are not there yet. We need everyone contributing the data and building this informatics resource.

TB: Everyone contributing from around the world?

SK: Yes, definitely so. It has to be worldwide if it is going to work. It won't work if just from people in the United States join this effort. I don't know what the numbers are for psychology, but for neuroscience in this country we have approximately 25,00 to 30,000 people and worldwide there are 50,000 to 55,000 neuroscientists. Some of them are psychiatrists and neurologists. If we could bring all of the information, all the data, from all these brain scientists together, we would have extremely valuable data.

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

SK: Not at this time. I appreciate this opportunity to review my scientific activities with the ACNP.

TB: Than we should conclude this interview with Dr. Stephen Koslow. Thank you for sharing all this information with us.

SK: Thank you.

PAUL LEBER

Interviewed by Thomas A. Ban
Acapulco, Mexico, December 15, 1999

TB: This will be an interview with Dr. Paul Leber* for the Archives of the American College of Neuropsychopharmacology. It is December 1999; we are at the annual meeting of the College in Acapulco, Mexico. I am Thomas Ban. Could you start with by telling us about your background and education?

PL: I'm the son of a physician, and I think it was understood from the time I was very young that the only sensible career was probably one in medicine. I toyed with other ideas but basically, I think the long-standing parental model held and before I knew it, I was a physician.

TB: That was when?

PL: I graduated in 1963 from NYU School of Medicine, but I was ambivalent even then about what I wanted to do. I thought about it because I had taken what was the forerunner of MD, PhD. programs. I had a medical sciences degree and during that period, approximately two and a half years, I spent in the lab basically looking at the biochemistry of myosin ATPase. And that, I say, represents my ambivalence. I already had been on the wards at Bellevue and found the clinical care of patients in a charity hospital not at all that I had thought it would be. Having seen medicine through the eyes of my father, who was a practicing physician –if you'll recall the book, *The Last Angry Man* by Green, describing the life of a practitioner– it was not what I saw in the wards of a big city hospital and I decided that there might be other ways to make use of my background.

At that time, Lew Thomas, who was the Chair of Medicine at NYU, had started something called the Honors Program that was an attempt to get young medical students who might otherwise have gone directly into clinical practice, into the medical sciences. This was in the post-Sputnik era where there was great interest in developing research capability in all areas and it was fairly easy to get grant money from the Federal government. I think that stimulated the general belief that anyone going into practice was probably foolish, that the real career in medicine wasn't to become a clinician but become an investigator. I think that to some extent, I got caught up in that role model there and that's how I shifted away from the idea of being a physician. It was the first time I'd probably thought about what the distinction meant between the role of a physician and an investigator. I think there was still a bit of a sense in me that

* Paul Leber was born in Brooklyn, New York in 1937.

physicians were different and special, as they were at least in my father's eyes. He probably struggled a lot harder than I did to get things in his life. But some of the bloom was off the rose by the late 1950s or early '60s, and I think the feeling was that just being a clinician wasn't all that unique or different. The feeling was that we were science and medicine and solving mankind's ills through chemistry was somewhat appealing to me. So I ended up, again finding myself half a biochemist and half of a fledgling physician advised by most of the people, who knew me at the time, to get a very strong clinical background.

TB: Where did you do your internship?

PL: I interned at Johns Hopkins in Baltimore. Spent a year there and I usually say that I still owe them for that year, during which we took calls on rotation arduously when we were on the ward. I came back for a year of residency in medicine at Bellevue and by then, I was pretty much sure that the actual delivery of healthcare at that level wasn't what I wanted, and I went into pathology. Pathology at that time was the kind of place where people who couldn't actually relate to patients went. It was a way to do the basic science of medicine without having the demands of patient care. And patient care in the charity hospital system, if you really want to do it well, was a full-time activity. It was the actual care of patients plus rounds-man-ship that meant you devoted your life to doing it unless you became an academician and did research. And to many of my friends, it seemed more reasonable to do it in an area where you could regulate your university academic responsibilities, as you could in pathology. Basically, the basic science you ended up doing was the same, at least so I thought early in my career. It turned out later that I recognized the control was very much in the hands of the clinicians and not pathologists. And one of the reasons I eventually, I think, switched fields is that I really didn't want to work for other physicians, a strange comment. But at the time, Pathology offered a lot of advantages. I didn't want to quite give up medicine but I wanted to take advantage of what I had learned before and pathology seemed a reasonable compromise. It's true, pathologists are somewhat isolated but in the American set-up being a clinical pathologist afforded you some contact with other physicians that at one time was seen by me as a great advantage. Subsequently, having worked for surgeons and others, I adopted a view that pathologists were the physicians' physicians. Unfortunately they are in the sense that a valet is a gentleman's gentleman. So there was a fair amount of service to other people and not so much control. And I started to drift towards psychiatry.

In about 1969, I went to State University of New York at Buffalo following actually Bob McCluskey, the guy that I had worked under as Chief

Resident of Pathology, who went to Buffalo and became Chairman of the Department of Pathology of the University Hospital. I went to Buffalo as the person who was going to coordinate the courses for the second year students in both medicine and dental school while doing also some work in the laboratory. While my major academic responsibilities were not in the clinic or even in the path lab but running the courses I found that we were having a lot of difficulty with students. This was the time when they were trying to increase the number of students being graduated from medical schools. There were many programs to bring disadvantaged students into the University, and the school was not doing all-that well. And one of the missions obviously, of the pathology department, which was sort of the introduction to medicine, was to improve the school's Board scores. I got involved in this, and we managed to improve the scores but we still had a block of students that were doing very badly. And I have to say in dealing with them on the faculty at Buffalo and discussing problem students that we were ordered to pass to the next year, I became impressed with my ability of handling them as well as anybody else. This was one of the factors that contributed to my drifting from pathology to psychiatry. Added to that was the fact that I'm married to a clinical psychologist.

TB: So, you are married to a psychologist?

PL: She was sort of analytically style trained, and I always had what I thought was common sense about things in psychiatry. But in any case, it was probably a lingering idea to become a psychiatrist. Anyway, McCluskey left Buffalo in 1971. He went to Harvard and assumed the Chair of the Department of Pathology of Children's Hospital there. Although I had no interest in pediatrics per se, it seemed appropriate, when offered a job, to accept at 'America's best medical school.' My life was pretty pleasant in Buffalo. I had a lab. I had my teaching that I liked. I was doing renal pathology in those days that was the area I had moved into. But there were also some hindrances as for example the horrible winters. Anyway, for whatever reason, I ended up on the faculty at Harvard Medical School in the Department of Pathology. But after three years of working for surgeons and working in basically a position where I didn't quite fit in the system, I had become fairly disillusioned with what was going on in pathology and discovered that I really didn't like it at all, and began to think what else I might do. We always joke about people having midlife crises. I guess I changed careers, and I think my experience in Buffalo plus exposure to my wife, got me interested in what was going on in psychiatry.

TB: So, you decided to do a residency in psychiatry.

PL: By that time my experience in pathology and my understanding of some reductionistic explanations in medicine made me increasingly cynical about what objective medicine could offer. I think by then I was convinced that much of medicine was practiced on the basis of old wives tales, told from one clinician to the next. A lot of what we did was what we did because our professors did it. Pathology, like Psychiatry, shares a diagnostic system that is taxonomic, authoritarian and passed down on the basis of convention rather than real understanding. And even though I didn't realize all of that, I saw Pathology as a discipline that had reached its peak in the 19th century, in histological pathology and I wasn't really that satisfied with that. Anyway, whatever the real reasons are, I decided, with my wife's acceptance of this, perhaps she could have saved me and I would have never been a psychiatrist, to retrain. And that was in about 1974.

TB: Where did you do your residency?

PL: Where I landed up doing my training was probably just chance. I began to look at opportunities but I had been through enough residencies in internal medicine and pathology, to be a connoisseur of what one really needs. I recognized that simply being on call all-night and having a very tight schedule, just makes you very tired and don't teach you much. So, I ended up at the New York Hospital, Cornell, in the Westchester Division which is one of those hospitals, all very much alike, built at a certain period of time in the United States. They have large, pleasant campuses that remind you of something between a country club and a private school. They really were built at a time when psychiatry was seen as an asylum for those who could afford it to remove themselves from the Sturm and Drang of everyday life into a commune with squirrels and nature to take a rest cure modified by changes in fashion, offering water or hydrotherapy or whatever the fashion was of the time. But basically they were asylums in the sense of gloom and doom. And this particular hospital in Westchester had, at that time, perhaps 240 acres. It was very attractive and had the added advantage, since I came with children and a wife, that it would give me a house on the grounds. I didn't get much salary but basically I could afford to retrain from what I got, and that probably determined where I went as much as anything else. I didn't necessarily want to go to a place that was a big city hospital again. So I ended up in Westchester at the time when it was undergoing a transition. It was an eclectic background that I got at Cornell. In fact, it surprisingly had gone through a period where it had supported almost anything but analytical views. One of the people who was at Westchester before I came, but had already left by the time I got there, was Paul McHugh,

who was an advocate of the phenomenological school that was competing with the analytical. These were the dying days of psychoanalysis although it would have been hard to say at that time that psychoanalysis was dying. But eventually it happened at Cornell. In any case, I was hired by a group of eclecticists who were still there after McHugh had left. But then at about the very same time Bob Michaels brought the remnants of the Columbia Psychoanalytic School faculty to Cornell. So it was a very strange time. We had on the faculty people who basically ascribed to Jasperian phenomenology mixed in with people who were card-carrying doctrinaire analysts. It was so a fascinating time. We had the psychoanalytic faculty coming in who wanted people who got directly into psychiatric internships without probably ever taken care of a patient, So, we had people coming in without any background in medicine mixed with a lot of older people among the residents who, like myself, had come from other fields and decided that a more holistic view of mankind was worthwhile, and were re-training. Then Otto Kernberg came.

TB: When did he come?

PL: He came towards the end of my last year. I did my whole psychiatric training there, three years. But by the time I completed my training I was totally disillusioned with psychiatry. I had dealt with a number of the prominent people in analytical psychiatry. Their methodology always left me somewhat aghast. They would say let me have two TATs and a Rorschach, and I'll tell you whether a patient is schizophrenic. Now when everybody knows that patient is schizophrenic on the basis of some common conventional code it's fine but when you have somebody who is a little peculiar and they decide on the basis of some response to a questionable test, I was somewhat offended by it. And by then, I was finished with the whole concept of the psychoanalytical model and was much more interested in biological psychiatry. It had nothing to do with the place. The place wasn't biologically oriented at all. The one unique thing that the training program had offered was the remnant of McHugh's influence. They spent an awful lot of time talking about the phenomenon. For me the most useful part of the training was sitting around in a room with my colleagues, looking and talking to patients, watching their behavior and then afterwards, discussing what we saw. If there was any group that was against explaining what they saw, it was the group of phenomenologists. They simply wanted to describe what they saw. So that was very useful. But all what the analysts were interested in was to get us into analysis.

TB: Did they get you into analysis?

PL: I spent some time doing analytical training, and if anything, it embittered me. Well, the first thing they said to you when you didn't do something

they liked was that you have counter-transference. I once pointed out to one of the professors that he had himself a counter-transference reaction directed at me. Now, of course, psychoanalysis wasn't so dominant in the program that they could order you to go into analysis but if you disagreed with them they tried to make you feel that something was obviously wrong with you. It was a kind of catch 22. And it was difficult to deal with them because they still had some power. What they did convinced me that I needed to get back to a real hospital.

TB: So, you wanted to get back to work in a real hospital.

PL: I was interested in liaison psychiatry because it, again, was a way to make use of my background. I still liked many aspects of medicine. So I ended up trying to get a job in liaison psychiatry. There were some openings available but not in locations I wanted to move. So, I went to Bellevue. It was the one place where I still had many people that I knew quite well in the departments of medicine, physiology and pathology because I had been there for some 13 years on and off. It was like going home.

TB: Could you tell us something about Bellevue Hospital at that time?

PL: All right. I can elaborate a little bit about Bellevue Hospital Psychiatric Service at the time. I actually had been there twice. In 1965 when I was a resident in medicine, I spent some time in psychiatry there on a rotation. This was before the Health and Hospital Corporation took over the city hospital system. At that time, the Bellevue Psychiatric Hospital, which had a physical bed census of 430, used to run in-house, at any given time, perhaps 600 to 650 patients. If you walked through the wards at night on the upper floors where the acutely psychotic and seriously ill patients were housed, you saw mattresses spread along the floor because the hospital just did not have enough beds. The psychiatrists could not serve the large mass of patients who flowed through Bellevue because the hospital was the last resort for almost everybody from everywhere. When a major New York hospital, like Columbia or Cornell, refused to admit someone, the patient was brought to Bellevue. If there was any hint that the patient might not be a medical patient, and patients often were not, they were sent up to the psychiatric hospital where they had sort of a *prima facie* evaluation but little else. A lot of people were misdiagnosed for psychiatric patients who weren't, and you actually did some good by correcting the diagnosis. Well there are many interesting internal old Bellevue stories some of them probably apocryphal more than real but basically there was always a struggle because of the enormous load, beyond everyone's capacity to cope with. Things were somewhat improved when I came back in 1977. After the Health and Hospital Corporation took the hospital over they were trying to put caps on the size of the wards but clearly, they

would still have overflow. And there was just not sufficient support. We didn't have a psychiatric nurse on our ward. The ward originally had a U-shape, and we were supposed to have two nursing stations, one facing down each arm. Because we didn't have staff, we could not have aides, so they closed one of the nursing stations. That meant that one arm of the U was basically unsupervised bedlam where assaults and various other things took place. I once went to the Medical Director of the hospital to complain after a particularly difficult morning where there had been a fight in the dining room and some of the inmates had broken off bits of the edges of the tables, and carving on the tables knife-like devices. The Medical Director said well, Paul, you really should be concerned because you are responsible.

TB: What kind of patients did you see at Bellevue?

PL: Well when I was there in '65 as a medical resident, I would say that the vast majority of patients admitted to the hospital were classified as schizophrenic. But, at that time, American psychiatry was in the bloom of its analytical mode. Diagnosis was dimensional and based more on somebody's feelings of what a patient had. So all chronic patients were just immediately called schizophrenic. We didn't have time to do a mental status. We were just overwhelmed by very bizarre presentations, some of which were medical and some of which weren't. Things had changed a bit by '77 because the analytical movement was losing grounds.

TB: Were you aware that DSM-III was just around the corner at that time?

PL: Oh sure. We knew that DSM-III was coming already when I was in Westchester.

TB: You started to tell us that most patients at Bellevue were diagnosed as schizophrenics. What about affective disorder?

PL: We had no patients diagnosed with affective disorder. We got the patient from the New York bus terminal, the ones who were found wandering, who were bizarre. We got the homeless, those with chronic brain disease, people who were disadvantaged. We didn't get a representation of the psychiatric population. If you got to Bellevue, the only one drug you could get there was Thorazine (chlorpromazine). It was usually delivered IM in large doses so that people would be knocked out. I didn't have myself a great knowledge or experience with drugs. I had been brought up on homeopathic doses of haloperidol in the Westchester division where the last thing they wanted you to do was medicate someone. As a matter of fact the phenomenologists were treating their patients with barbiturates for a few days to see whether or not the psychotic process would disappear, so that we might see the underlying personality.

TB: So the situation at Bellevue in those years was pretty bad.

PB: Yes, and after spending almost a year at Bellevue, I decided that I'd had it. Dealing with the frustrations of a city hospital system, living in Westchester and having a small part-time practice in midtown was really just not what I had retrained to do. Liaison was an area in which most of the people wanted to get Fellows to do the work but it wasn't an easy and sure way to establish yourself. In fact, you often ended up in a consultative rather than a truly liaison system. And just at the time I was wondering about what I should do I learned about a possible job with the FDA. The FDA was at the time a place that people with the exception of those who worked there, knew little about. It's an organization, that at least until the time of David Kessler, operated more behind the scenes than in front. And I came down to Washington in 1977 to look at the job.

TB: What made you decide to take the job with FDA?

PL: As I had said earlier, the FDA was as much an unknown agency to me, as to anyone else. I came to the FDA not because I had a cause, but because it seemed to be a good place to make use of my background. It was a place for someone who knew something about medicine, pathology and psychiatry. I felt in a way that would allow me, in midlife, to do something that was constructive and useful. And I have to say the FDA has been a career for me. I've been there 16 years. It is probably the place where I've learned most and felt I was doing the most. I know now very clearly, how little one really can do within a relatively weak mandate that it has.

TB: So, your motivation was to do something constructive and useful.

PL: I think motivation is complex and it isn't, what caused me to go to the FDA, but, what I did once I got there, which I think is important. I went into a job that I suppose some could have treated as a 9 to 5 job, doing the reviews and leave. I work 60 to 70 hours a week. I like what I do. I find the area I'm working in fascinating. I'm involved in it because I see it as a microcosm of our society where I can make something happen that's good, do the right thing. I'm imperiled to do the right thing. And what I can add is that in doing the right thing one has to be as an umpire, who is never that popular because when he makes his calls, he is always offending someone. I must have been the subject of several editorials in the Wall Street Journal of not caring about patients and of being the industry's boy. But I know that I care about the patients by carrying out my job under our law that even if in a somewhat paternalistic way wants to make certain that the drugs are reasonably safe when used under the conditions they are recommended. But what I like about the agency is that it's a place that tries to do the right thing, with a fairly clear set of directions. My response to the libertarian argument to let the marketplace

to find out whether a drug is safe, and tort liability to handle it, is that our society hasn't agreed on that compromise and congress is free to change our laws anytime it wants to do it. Personally, I think it would be a mistake. I actually think it's a very good idea to have rules of pre-market clearance that establishes that a drug is not excessively dangerous, that it probably has a reasonable risk benefit ratio, and so on. It's intervention of government but that's the nature of our existing laws. It's easier for me to enforce it because I believe in it. It doesn't mean that I don't have moments of tension where I see where the law doesn't exactly fit.

TB: Can you give any example when the law doesn't exactly fit?

PL: If we have to tell some patient with advanced ALS, look, we're concerned allowing you to have access to this experimental drug for which we have no evidence of effectiveness.

TB: I suppose the same applies to AIDS?

PL: When I came to the agency, AIDS was just about beginning to be identified as a distinct syndrome.

TB: Before moving any further, could you tell us what the mandate of the FDA is?

PL: If you look back over the last 100 years you see a pathway to produce a government that is protective against the forces that may take advantage of the consumer and get the government to step in and do something. It's related to the philosophy that government has to protect the citizen from situations that are beyond the citizen's control. It's a kind of delegated narcissism, that the government can do more than actually it can. Congress is always passing a new law that adds greater protection. To a certain extent protection, because of the way it's sold, looms larger and seems to have more power than it actually has. The task is to make sure that all drugs are safe and effective for use. But what does that really mean? No drug is safe and no drug is fully effective. People want things that they haven't thought through carefully. So we talk about offering protections without knowing all that is involved. But there certainly has been a trend in this country to produce a society where individuals are protected from the unlimited power of certain groups or institutions. And no doubt it's the role of the government to do that. So, more and more powers were given but also more and more demands were placed upon the agency to help ensure the safety of the consumer, at least in terms of the products that society allows to be marked as food, drugs and cosmetics. Now whether or not the agency can cope with the task given considering the number of products out there and given the number of opportunities for things to go wrong, even if one is careful, is another matter. You see many things can go wrong with a drug even if you do a wonderful job.

And we have a public that is inflamed if anything goes wrong. They are good news stories regardless whether they have any basis. And we have a public that is inflamed by these stories.

TB: Could you say something about what you have been doing since you joined the Agency?

PB: I came in 1978 and I was assigned just a medical officer. Within a year, I became a group leader. Actually, I became a group leader because I was thinking about leaving. It was kind of boring what I was doing and the then head of the department said look, you're bored by the job, tell you what, why don't you become a group leader and try to do something to make it better. And I was involved with antipsychotics and anxiolytics, and somebody else had antidepressants. I wasn't even involved with hypnotics. We also had Tom Hayes, who wasn't a psychiatrist; he was in neuropathology. We may have had one other psychiatrist in the unit. And I began looking at trial designs, and it became fairly obvious to me that one can't conclude anything from trials that fail to show a difference. Bob Temple was making a similar point, and we thought that if we were going to make a judgment whether a drug worked, we ought to make it on the basis of the difference from something because finding similarities prove little. This didn't come from me. It came from Modell who had taught it in pharmacology in the 1940s and 50's before we had efficacy requirements. They said, look, you shouldn't conclude anything about a clinical trial unless you have the ability to discriminate the active substance from the inert one. That's absolutely the basis of the argument. So I found myself in the position where I could start imposing that the law says that one has to be able to conclude that the drug is effective and that one is not supposed to conclude that on the basis of evidence that is ambiguous. It was the need to provide evidence that led to the use of placebo in clinical trials. Then, by 1985, we developed a new trial design that led to greater flexibility. That document pretty much summarizes what I think were my contributions in the area of designing clinical trials.

TB: So, by 1985 a new trial design was developed that led to greater flexibility.

PL: At that point, we got caught up in AIDS and the desire to have early access to treatment became dominant and that undermined our ability to find critical evidence of a difference for a new treatment. We ran into this issue a couple of years ago with a football player for the Jets, Dennis Byrd, who was injured in a Sunday game at Giants Stadium. He was quadriplegic after the accident and ended up getting a drug product made by FIDIA, one of the gangliosides. He could get it because at that time it happened that we had something equivalent to a compassion protocol that allowed the use of a drug before its effectiveness is

conclusively proven. And while the Dennis Byrd case was going on we had a randomized controlled trial that involved randomization of people with spinal cord trauma. Now Dennis Byrd happened to do fairly well, whether because of the steroids he got, the ganglioside or simply by chance I'll never know. But the mere knowledge that this guy had access directly to that drug without running the gauntlet of randomization, created a humane cry that threatened the investigators doing the trial. I got some of the most compelling letters I've ever seen saying, how could my child be forced to go through randomization when this guy with connections didn't have to. Well a lot of the diseases that we are dealing with not so much in psychiatry but in neurology have no effective treatments and as a result people with those diseases say well, what have I got to lose given the active substance; I have the right to ask for whatever it is; it's my life. They say I want the new drug now; how dare you stand in my way. And with this kind of arguments the issue of autonomy that dominates thinking about ethics in medicine today becomes a central issue. Now all this sounds very grandiose because if it's your child is in pain you want to get access to the medication without randomization.

TB: How does the agency handles the requests?

PL: What people really want is access to a drug and what the Agency decided that everyone should at least have equal access by randomization; 50% probability of being exposed is better than none.

TB: Are you in a decision making position?

PL: I'm only a small cog in a very, very large institution that is making decisions with several tiers of supervision and safety nets and the like. I may offer an opinion, but my opinion isn't necessarily taken. Actually, most of these drugs that I'm accused of approving against the interest of the public I don't even approve. All I do is forward a set of recommendations offering my view about whether or not the evidence presented was gained from sources that nominally look OK and whether or not our review supports it. I usually try to defend what we do, not because I believe that I need to defend it but because I think the institution has to be able to explain why it took a particular position.

TB: What is the most common accusation?

PL: The most common thing that is said about the people in the FDA is that they're in a poorly paying job and after they work there a few years they get bought by the industry and move over to, well paid jobs. But whom are they talking about? Well. Name one? Supposedly, there is a string of people from the FDA, who supposedly moved over to industry and then spend, their time helping the industry prepare their drug applications. I'm sure that every institution has its ogres and has its angels. I'm sure that

there are a great variety of individuals. The vast majority of people who work in my unit haven't gone anywhere. They are still there. I'm there 16 years. The head of the neurology group is there 11 years. The head of the psychotropic group is there 11 years. They are the people who're making the major policy decisions. The only ones I know about, by the way, who went to industry in high paying jobs recently, in our area, were lawyers. They go to industry. They go and work for other corporations, but they were never involved in deciding whether drugs worked or not.

TB: Let me ask you what do you think of the common complaints that complying with all regulations interferes with work?

PL: It comes down to people on the clinical side saying well we've got to go through all these good clinical practice procedures now and spend so much time filling out papers that we don't have the time to look and listen to our patient to make those key discoveries that were made through close observation of patients. And people within the industry are saying that I used to work on the bench but now with this good laboratory practice procedures I've become a manager who's trying to ensure that every piece of paper gets saved so that we can pile up all these papers onto huge trucks which go off to the FDA and all of this is getting in the way of being able to create and design. I don't believe in any of this. The idea that the physician looks at the patient and says, aha, this is a new syndrome, I don't believe. I think a lot of this is political polemics. There's no doubt there is plenty wrong with regulation. It's like Churchill's line about democracy. It's a lousy form of government but there's no better.

TB: One of the drugs in psychiatry that was affected by regulations was clozapine. I know that you had been involved in the clozapine story. Could you comment on that?

PL: Clozapine is a good example of a drug that astute clinicians recognized that it might be different than other drugs. The problem was that until there was evidence given that it was different there was little one could do about it. And had it been a drug that hadn't been associated with agranulocytosis, probably it would have been approved and no one would have had any knowledge about whether it really was better than any of the other drugs, except by word of mouth. Because of the high risk of giving clozapine it was necessary to show that the drug might have some advantages over other neuroleptics. This led to the demonstration that it was an effective treatment in patients non-responsive to high doses of haloperidol, and that was actually to the advantage of the company that was manufacturing the drug. I don't know how good really clozapine is because all I know now is the testimony of people who apparently never before were able to function in the community and now are able to do.

But at least we have some basis now to believe those stories are true on the basis of the evidence that came from a controlled trial. I wish there were ways to get long-term outcomes to know if the findings of that study are really true. At the time when the clozapine patient managing system was put in place, I don't think it was our intent any way to restrain trade. It was simply a way to ensure that there would be no patient treated without monitoring leukocyte counts. We were very concerned that we might have one of those public health disasters. It ended up that several people interpreted it as an attempt to restrain trade, and we had other parts of our own government examining it. Eventually the Federal Trade Commission, I believe, impelled Sandoz to adopt a more open system of distribution. The more I think on the clozapine issue the more it seems that it had created a new treatment resistant inpatient category.

TB: Are you saying that clozapine created a new diagnostic subcategory used as an indication by the industry?

PL: Absolutely. No doubt we may have created an indication that doesn't exist. I don't feel all that badly, however, because a good part of psychiatric diagnosis, we all know, is nothing more than people agreeing that they will call the dough of nature what they want to call it. I'm still trying to find out who said that a good part of psychiatric diagnosis is taking a cookie cutter to the dough of nature.

TB: I don't know. I haven't heard that one. Some believe that the aim of diagnosis is to carve nature at its joints.

PL: I think that we may have created a subgroup that is nothing more than the tail of distribution. It may not be constant. I have no idea whether it breeds truth, but it was created by our attempt to balance benefit and risk. It may turn out that what we did was not a wise thing to do, but I think given the information we had at the time, it was a responsible thing to do. That doesn't mean that other people could not have done it differently. There is always more than one way of doing things. We try to find the right way, and anyone who disagrees has a variety of ways to disagree with our way. We're obviously working in a world where there's absolutely no certainty. You're always making some kind of judgment, you're always trying to find a way to accommodate a variety of forces, a variety of beliefs, and you are always trying to do the right thing to work within the restraints of the law in the time you live in. And I'm sure that you cannot possibly satisfy everybody. Clearly, the aims of every industrial developer of a drug are not the same as of the patients who would like to have a perfect medicine, at a low price available instantaneously. They are incompatible goals. It is probably not possible to have drugs that

are reasonably safe, adequately labeled, unlikely to cause harm, at least in excess, without having regulatory controls.

TB: What do you think about current attempts of having quality of life as an acceptable measure of outcome?

PL: Well, quality of life, I've always thought, is a grandiose, sweeping statement. We're all interested in things like beauty and truth. We all demand it. The problem is we don't all know it when we see it. I think quality of life is a very valuable goal. The problem is that I'm not sure you can measure it when you're talking about a particular disease entity. You certainly would like to have measures of global outcomes and general benefits or something of that sort. The problem is when you call it quality of life. A lot of the quality of life rating assessments, as I understand it, were developed first by social health planners who were working across a spectrum of illnesses and disabilities with the objective to decide where to put societal funds and energies. I guess if you want to compare the disability of prostatism with that of breast cancer, with that of chronic schizophrenia, having some measure that is not disease specific it makes some sense. From the standpoint of regulators who are interested in whether or not the drug is effective for a particular disease, quality of life measures are more questionable. It would be more relevant to get something in terms of the impairments and disabilities associated with that particular disease entity. I wouldn't call it quality of life. I would go out and find what it is in that entity. I guess I'm a little bit concerned of anything that's too global, sweeping and grandiose a statement that is on everyone's lips. It's a good way for third party payers to be snookered into paying for more expensive drugs. But it's very hard to know how one weighs the various elements that go into quality of life; they may include rating assessment on anything from how much one enjoys leisure time activities, to whether or not one has adequate housing. I think we are better off using measures of the pathologies, disabilities and impairments that we are dealing with than quality of life measures.

TB: Regardless of the end-points used, if I understood you correctly, you are for randomized clinical trials.

PL: I often wonder how anyone can adjust without a randomized controlled trial for the fundamental differences that could arise in outcome research between the reason people are treated with the drug and the disease they have and the nature of the drug treatment they receive. I guess I'm an old stick in the mud, I like randomization and randomized control trials, not because I believe that randomization solves all evils, it just minimizes the biases we don't know about. Short of randomization, I don't know how anyone guarantees the differences seen are due to the nominal application of this one thing you're interested in.

TB: What are your thoughts about the need for comparative studies?

PL: I'm always afraid of comparison. I mean how to compare new drug products I think is one of the biggest problems we face today in the wars that are going on cost benefit and cost effectiveness. In some ways a new drug starts with a handicap and not only because the developing of a new drug is more expensive in 1990 than it was in 1980. How do you get on the market and recover your costs in a contracted world? You have to say you're better than somebody else. What makes you better? Well are you better than every product in the armamentarium or better only than some? What are you better for? What are the dimensions on which you make comparisons? There are literally an infinite number of ways you can compare drug products. You might compare the quality of effects, their intensity, their times of onset, or their duration. How do you pick which of those dimensions you're going to look at? Well the clever marketer of a drug identifies an area where the market would stand improvement and shows that his drug is better than drug X. So in case of an antipsychotic he might compare the effect of the new drug in producing EPS than haloperidol that has a probably well deserved reputation for causing a lot of EPS. Is it fair, therefore, to conclude that the new drug is better than antipsychotics in general because it beat haloperidol in producing EPS? How do you know what an equally effective dose of two neuroleptics is? Somebody says 10 mg of Haldol is worth of 6 mg of risperidone whereas someone else would say 20 mg Haldol is worth 6 mg of risperidone. And probably the biggest problem is that very often people will pick the conditions of comparisons to suit their goals, and we, as regulators, are going to get involved in this kind of problem. One just has to be very careful that the comparisons are fair

TB: What are your thoughts about the use of fixed or flexible doses in clinical drug trials?

PL: You'd probably want a fixed dose but these days fixed dose is coming into a lot of criticism and with good reasons.

TB: What are your thoughts about sample sizes, the need for large sample sizes?

PL: They are certainly going to be necessary, but the methodology for doing them fairly in a way that gives you information that doesn't mislead you is going to be tough, and I don't think we've worked it out yet. Well the basic problem is that we don't know the etiology and pathogenesis of most of the phenomenon that are subsumed under the diagnostic group of recommended conditions. Not only that, it's not clear whether a medical model is really the best. I'd be the first to acknowledge that one of the difficulties with taking the medical model very seriously in psychiatry

is that the medical model grew out of a belief that the cause of disease was univariant, that you had a pathogen that interacted with a host and generated perhaps some psychopathological features. The concept of multifactorial, polygenic model doesn't suit too well the medical model which says that these are like medical diseases that have their etiology and their causes. Now for purposes of making progress, I always thought DSM-III was a great idea because it allowed people to use a common set of definitions. It allowed people at least to agree on what they were describing. It has created the possibility of doing experiments. You can at least recapture or resample and you can find out whether the populations are biologically homogenous in terms of their response or not. I'm not sure whether DSM-III, DSM-III-R or DSM-IV are real advantages to anybody being labeled or just another taxonomic system. But again, I'm talking about this from the point of view of someone who wants to develop a treatment. I want to be able to communicate what that treatment is for in a way that other people will understand.

TB: So, you are in favor of the DSMs?

PL: For communication purposes and I think to that extent, you're stuck if you want to decide whether the labeling is accurate and not false or misleading. How would you communicate without it? It would be idiosyncratic and impossible to communicate if we would not use it. Clearly, these drugs aren't used by psychiatrists alone but are used by GP's for a variety of things. We felt it would be very useful if we could give them a fairly standard description and that's all it's intended to be. And of course, in this society, technically a physician is free to use any approved drug for any reason they want, provided it's allowable under the jurisdiction of safe practice. That's an issue people are increasingly confused it seems. People feel that if a drug had been licensed for a certain use, then one is on tricky grounds of using it for other indications.

TB: Yes.

PL: We have frequently been chided for failing to approve drugs for uses everyone uses them for. Xanax was widely used for a long time in panic disorder without any labeling. We were concerned about higher doses and the difficulty withdrawing from the product, and we decided that it would be useful to examine these issues first before handling the claim for that indication. The argument was that panic was always subsumed within anxiety or generalized anxiety and people could treat it any way they wanted. In fact, there are some investigators who believe that panic disorder doesn't exist and if it does exist, it is just as treatable with other benzodiazepines as it is with alprazolam. But all of that being said, there is certainly an advantage to us to be able to make clear cut distinctions

between what we have been handled closely and have evidence for and what is common usage for which there may or may not be evidence.

TB: What about the use of imipramine in panic disorder?

PL: Why has imipramine never been approved for the treatment of panic? Clearly, it was one of the drugs that Klein recognized had an effect in panic. It probably does work. Well no one ever assembled the information and brought it to us and that is simply the reason. We don't go out and tell people that they should ask for approval of something. They have to actively seek something from us as an agency, and I think that's not well understood. Now we might or might not be willing to approve it depending on the quality of evidence. There are a lot of things that are widely used on the basis of belief for which no one can adduce evidence. In fact, I know of drugs that have been around for 10 or 15 years, widely marketed throughout the world and I know the sponsors have tried to produce the evidence that show they work and they are unable to. A lot of physicians believe some of those drugs work. Now until we see the evidence, I won't know but it always dawns on me that there are many reasons why drugs appear to work. It's the old joke use the new drug fast before it loses its power to heal. Another is, treat people very soon before they get better spontaneously. It's a combination of those two things. I don't know what accounts for it. But a lot of illnesses, for example, people with mild depression, do get better. The power of the FDA is to control the initial marketing of the product. The power is, therefore, to control labeling. The power is to try to keep the sponsor within the framework of labeling. They can't go beyond it, even if the drug is widely used. Now you can argue, that is a disservice to the community as a whole. You can also argue that if the firm wants to develop a claim beyond the one they have, they can collect the evidence as required and allow, therefore, for regular scientific basis for which the drug works rather than simply the observations of physicians. But there is this leak and it might happen that the drug will come on the market for a particular application and get used more broadly by people.

TB: But what would happen in case of a cardiac death of a patient treated for panic with imipramine?

PL: Then, if you go to court, if you're a professor, you could probably say I do it because of my experience. If you're not you could say there is a whole body of literature supporting the use. You could probably point out in a court of law where you're defending yourself for malpractice that I with the informed consent of the patient decided to use it because the patient could not tolerate alprazolam and now we've had this misadventure. It didn't turn out the way we wanted. People have this odd kind of belief the

FDA has control access to the market but all sorts of things get onto the market by other routes. There really is a body of information that hasn't been presented to the FDA in the form of a formal supplement seeking a claim; a marketer of imipramine might say well the drug is long since out of patent and there are generic forms available. Although we'd be willing to do it, they might see no economic gain in it. That still wouldn't prevent any practitioner from assembling the literature that supports the use and say here it's perfectly reasonable to use it. Now I realize that people and the legal system uses DSM-IV diagnoses and the FDA is hardly the final arbitrator of what good practice is. There are a lot of odd things going on because third party payers want to be able to spend less and that they will disallow expenditures for uses they feel are outside what we've approved and the agency is taking a very definite stand that its approvals speak to what the drug can be marketed and advertised for. The physicians are free and we could go round on this forever, I think there's even been pressure to try and get people to submit supplements so that we can approve drugs for additional uses if there's evidence, but it often turns out the evidence isn't very good. I think the agency ran into this when it did its drug efficacy review right after the passage of the 1962 amendments that were created as a basis for demanding proof of efficacy.

TB: Could you elaborate for us on the '62 amendment that led to the withdrawal of many drugs?

PL: There were thousands of products on the market but when they got finished, there were only hundreds. So many of them were marketed and there was no evidence and no one could produce any, so a lot of the drugs we had for treating dementia or dementia surrogates, or the treatment of depression, were banished. It doesn't mean they didn't work by the way; it's that no one was able to produce the evidence that met a minimum standard. You could argue that an armamentarium was better if you could have anything you want. I think that's good up to a point. If nothing works, it's fine to have a lot of products which are not dangerous but then if one drug works, you could make the case that having anything in there that doesn't work, eludes the armamentarium and is a threat, as it might be with an antibiotic that didn't work. But clearly, these are the issues people are struggling with right now. How do you get efficient evaluation of drugs? How can you do it according to standards? For example, if we were suddenly to lower the standards for proof for secondary claims, what impact would that have on the whole structure? You do need more than one. This is the other buffer. Anyway, I mean, clearly we aren't going to solve this particular problem because the one of standards is constantly undergoing review. In one breadth, you want

to be very sure that you know not only that drugs are effective that we market but we been striving for finding the conditions under which they should be used, find the differential risks in using them and subgroups in the population.

TB: Wouldn't you think that doing things in a standardized way, as for example using the Hamilton Depression Scale exclusively in all studies might have drawbacks?

PL: We haven't found ways around that. If you use the Hamilton Rating Scale for Depression only you can argue that certain types of antidepressants come up and others don't and then companies dump a whole lot of extremely useful drugs because they are not going to come out superior to the older drugs on the Hamilton Rating Scale. And if they don't come out superior, there's not going to be the marketing angle on them and the return won't be there. Some of the newer serotonin reuptake inhibitors may, in fact, look bad on the Hamilton. So we don't care. We've never said you can't approve the drug because they don't look good on the Hamilton Depression Scale. There is the Montgomery-Asberg scale and you can use that. If you come along with a new methodology that is untried and you're willing to take a chance, go ahead and take it.

TB: What about guidelines for industry?

PL: We've been encouraged to do that over the last decade maybe because people have argued that what the FDA wants is a moving target. So they wanted guidelines that tell them precisely what we will demand. Well guidelines are constricting. But Frank Young, who was Commissioner of Food and Drug, was under great pressure in the aftermath of the Sommer's Report in 1986 and said, go out and create guidelines so that we'll be able to tell them at the industry in advance what we're willing to accept as the minimum requirement. So in the process of consensus building, we built guidelines, talked to a lot of people, had many sessions and ended up with guidelines. I think if we had a drug that really stopped, for example dementia, we wouldn't need a guideline. But the industry demanded guidelines because they wanted more economic certainty. So a lot of the stuff isn't because I'm not able to tell if a drug works or not, but it's the question of what the industry wants. They'd like standards for showing that their drugs are better than other drugs because it isn't just enough to believe your drug is better than another drug but you have to show it. There's going to have to be some basis to promote a new drug and advertise it.

TB: But insofar as I know you don't have guidelines for that.

PL: Our law isn't a comparative law. We are not normally engaged in assessing whether or not you're better than another drug, only whether or not

you do what the labeling claims you do. No doubt industry would like it. Should we have guidelines for comparisons? How would you choose the comparison drug?

TB: So it seems that there would be difficulties in providing acceptable guidelines for comparison studies and for the time being we are stuck with placebo-controlled studies. As you know there are some objections of requiring placebo control.

PL: Well industry does not want it because they are worried that the size of the treatment effects seen in most antidepressant trials is so small.

TB: Yes, indeed.

PL: Oh, I think it is getting smaller, that's why they don't want the added treatment. I mean ideally, everyone could be on cognitive treatment and the new drug should be an add-on.

TB: There might be also some other reasons why there are objections against the use of placebo.

PL: People don't like placebo because I think it requires you to take the patient who is ill and suffering and put them on a treatment that the investigator or physician knows, is unlikely to do very much. It may not do much harm but is unlikely to do very much good. If you believe there are active treatments out there, how can you possibly deny them access to an active treatment? Well that's fine if you knew your new drug really works but if you don't know your new drug really works, to me it's incoherent that you would be willing to put them on this new drug that not only may not work but be dangerous and deprive them of access to the standard treatment.

TB: How do you get around that?

PL: Well if you say the standard treatment doesn't always work and we know that's true in 30 to 40% of people, you want to put a patient on placebo because you want to find out whether the drug you are working with works.

TB: In the old days we did open, uncontrolled clinical trials to see whether a drug works and then small single center controlled studies but today partly as a result of guidelines like the FDA's we have this large multi-center placebo controlled studies in which all data is owned by the drug companies and the individual investigators have lost control about their own contribution to the data pool.

PB: Well that probably has to be worked out by the investigators in the trial that make their agreements with the firms. I'm sure that there are examples of where firms haven't behaved in the best interest of the public as for example by not publishing negative results. But I suppose academic investigators are no less likely to publish negative results than are firms. Maybe we ought to publish all results of all trials. But, again, I think all of

this is a question of looking at too few of the facets of a very complicated process. If you're going to develop new drugs, you have to ask who's going to do it. Since governments aren't going to do it, the private sector is going to have to do it. If the private sector is going to do it, why would they do it? I'm always struck by the fact there is a group that likes to think the FDA is a dupe of industry, and fails to acknowledge that we wouldn't have any drugs if it were not for industry. It's the nature of how we've allowed our society to develop a drug industry. We didn't say the federal government is responsible for developing drugs or the state government or something, costly public institution. We said we're going to let the *laissez faire* system work. People will come forward because of opportunity to make some degree of profit. It's true, we may make sure they don't make an egregiously excessive profit but basically it has to be driven by the profit motive. If that's true, industry cannot be seen as the devil and all bad. That doesn't mean that there aren't bad people in industry and it doesn't mean that at times industry doesn't do bad things but basically, that's where our drugs are coming from. Now the other side of the argument, of course, is that industry relies on government, that all this really comes from investigators who were trained at universities supported by the public. These people as soon they get trained, run off to industry, and industry is reaping too large a profit. Well those are all political questions. Is the drug industry a utility? Is it a natural treasure? We never missed the merchant marine and our merchant fleet so much until we had to move all the troops to Saudi Arabia and then realized we had no sea lift capacity. You can almost argue that the private enterprise of industry is a valuable societal asset, and you need to support them too. I'm not saying you need to give them rewards that they don't deserve but they can't be cast worldwide. They need you. You need them. This is not a conflict of interest, but a congruence of interest of a lot of different groups and that's why you need to help them do placebo control trials, because we all need to know whether a drug works. And without the industry having the resources to pay for it there would be no controlled trials, no randomization and drug development that meet current standards. I don't know how else you could do that. Academicians don't have the resources to produce the evidence that would be persuasive.

TB: So, you believe that without industry we would not have clinical drug development with our current standards.

PL: I've listened to Don Klein say many times, give me a drug and I'll tell you whether it works. Well I'm not so sure he can tell me in a way that I can hear. He may tell me he believes it works. He may, in fact, be right, but we're unable to listen to him unless he presents it in a form where we can

know in a public way if a drug works and that's where the confusion is. I don't see there's any reason why, in the midst of a control trial that uses placebo, the astute investigator, if they are so prescient and confident, couldn't tell the difference. Why is placebo so confusing to them? Why has the structure of the randomized control trial so undercut their ability to pay attention to patients? I don't think there ought to be a patient who left a controlled study without the equivalent of a narrative summary of that patient written by the PI, not his residents, not his clerks, not his co-PI's, not his nursing assistants, but by that PI who says I saw Mrs. Jones, admitted three or four nights ago, or whatever, and she presented with these phenomenon; I've treated her for six weeks and these are the things I saw and these are the things I didn't; I think she has improved. I can't, of course, know whether she was on a drug or not. I suspect she was on a drug because she had these things. These are the adverse effects she had. I think she did moderately well and sign his name or her name. We don't have that. I'd love to get that kind of a narrative summary on all patients, even if there are thousands of them. I can't see where the structure of the design would interfere with every clinician doing this.

TB: It certainly should not. What do you think the reason is that we got into this situation?

PL: If you really want to know what I think, it is that the guys who're talking about not being able to get done their work in the clinic or not being able to get to the bench, are the same people who are going to so many international meetings like these that they are on the tour and they don't have time to see anybody. I mean, I doubt whether they follow a patient. Patients need to be seen every day, don't they, or every week, depending on how sick they are and I don't think they're doing it. They are not in town. I don't really believe that the modern trial prevents people from being astute. Maybe the day and age does. Maybe everyone's life is so busy that they can't really see their patients and talk to them. It really doesn't make sense.

TB: Who is then doing the clinical trials?

PL: That's another thing. A lot of famous people put together consortia and they don't do the work. They take credit for the work.

TB: Does not NIH also create consortia?

PL: NIH has consortia of Alzheimer's groups they're supporting. They've not always had an Alzheimer's drug to run through it. But I think we do need clinical trial units standing everywhere ready to go when we need to them. And because you need big trials and want them done fast, you probably can't rely on individuals being able to assemble them. I also think there's

a great pressure for people not to have to go to physicians to get something they can treat themselves with.

TB: What are your thoughts about that?

PL: As you move toward that, there are greater risks. I'm struck with this with sumatriptan for the treatment of migraine. There are reports that some people who have taken sumatriptan died of subarachnoid hemorrhage. Would that be better if a physician would have prescribed it to them than if they gave it to themselves? That's a societal call. I don't know if I'd want to treat my own depression. I certainly wouldn't want to treat my own psychotic episode or my organic illness. But, I think what you find now is that in modern medicine you can't reach your physician. My daughter has an acute disk right now, and I'm the one who has ended up treating her for her pain because of her inability to deal with a neurologist to get pain medication. It's unnerving how difficult it was, and I can imagine anyone with any kind of story of distress has the same problem.

TB: Could you tell us something about your recent activities at the FDA?

PL: I'm struck now with this paper that came out in the *New England Journal of Medicine*,, an epidemiological study of the risk of connective disease in women who had silicone breast implants around Rochester, Minnesota where the Mayo is. They always do a lot on epidemiology and in this study they found there were increased risks. So the *Wall Street Journal* writes an editorial about how crazy the FDA was and Kessler in particular was making this multimillion dollar decision which paternalistically had prevented women who didn't have breast cancer but wanted to have access to these things on the basis of information which turns out to be untrue. Well they got it wrong. Kessler's position may have been paternalistic, I don't know, but there was no information. This is the first information that's really come out.

TB: What do you do in the absence of information?

PL: The view they espouse at any time represents a political viewpoint. I'm sure the guy who writes the *Wall Street Journal* editorials has his position about it. He'll latch onto anything he needs to make that point. This was a convenient one. It's not fair but it's an example of how it goes now. If we had real knowledge of exposure of all products we might be able to decide that for some individuals this or that has a relatively bad risk and all I would do in that case describe that in the label. I wouldn't keep drugs off the market, I mean, if the drug works, I mean, this has been our philosophy for a long time and it seems to have a reasonable risk factor, but you probably want it out there.

TB: On this note we should conclude this interview with Paul Leber. Thank you, Paul for sharing this information with us.

ROGER MAICKEL

Interviewed by Leo E. Hollister
Waikoloa, Hawaii, December 11, 1997

LH: Today is December 11, 1997. We're in Kamuela, Hawaii for the 36th annual meeting of the American College of Neuropsychopharmacology. This interview today will be with Roger Maickel,* a long time member of this organization and a long time worker in our field. Roger, where were you born?

RM: New York, on Long Island.

LH: On Long Island?

RM: On Long Island

LH: And how did you get to Indiana? Did you go to school there?

RM: No, no, no. I was a chemistry major undergrad at a small liberal arts college, called Manhattan College, in New York City suburbs, and graduated with a Bachelor's Degree in chemistry and said, I'm going to be a chemist and set the world on fire, or whatever. I had attended the Polytechnic Institute of Brooklyn in 1954, and when I graduated, I had a teaching fellowship that gave me my tuition in all of \$800 a year.

LH: Princely sum!

RM: Princely sum! Fortunately, I could live at home, which was a plus, and commute in on the railroad everyday. I spent a year there in organic polymer chemistry and decided that it wasn't my cup of tea. So, I took a National Science Foundation exam for fellowships; and I didn't get one, but I wound up on the honorable mention list. And, about May of 1955, I got a phone call at home from a Dr. Sidney Udenfriend.

LH: He must have seen your application.

RM: I found out later that the NSF honorable mention list was circulated. He was at a place called the National Institutes of Health, which, as a chemist I knew nothing about, I mean, absolute nothing! He said we've got some positions open and we're looking for young baccalaureates who want to go to graduate school. You can go to school in the afternoon or at night at a local university and you work for us at the NIH.

LH: While you're getting an advanced degree?

RM: Your work becomes your thesis. And, he did about a ten minute sales job over the phone and he said, "Why don't you come down for a visit?" His question, "Why don't you come down for a visit," didn't mean that I was going to get paid to go down there for a visit. It meant, "Why don't

* Roger Maickel was born in Long Island, New York in 1933. Maickel died in 2006.

you pay your own way and come down”. So I did and I went to this big imposing Building #10.

LH: That was the Clinical Center.

RM: The Clinical Center, the old Clinical Center. It’s gotten bigger.

LH: Oh, yes.

RM: And, I was interviewed by Udenfriend and by two other people, Steve Mayer and Sidney Hence. Hence, was working on the metabolism of reserpine, trying to isolate the metabolites from dog urine or rabbit urine. At that time reserpine had really just been introduced.

LH: And, I don’t think the structural formula or anything had been clarified.

RM: The structural formula was known, but they had no idea of the metabolism. Mayer had gotten his degree in neuropharmacology at the University of Chicago with Jim Bain, and he was working on the blood brain barrier. Mayer was a neuroanatomist and neuropharmacologist and hence, was a biochemical pharmacologist. Since I was a chemist I thought, oh, boy, the reserpine problem was the one I would like to work on. Udenfriend said, “Well, the laboratory chief won’t be in today,” and that was Brodie, “but, he’ll be in tomorrow morning and I made an appointment for you to visit with him 10 o’clock in the morning, stay over tonight”. So, at 10 o’clock in the morning, it was about the first week in June, right after Memorial Day in 1955, I went to Building #10 and I met this bespectacled, gray haired, whirling dervish, named B.B. Brodie, and we chatted for about 20 minutes. I did most of the chatting. Actually, he asked a few questions, and he said to me, “Well, which problem would you like to work on?” And, I told him, with great flourish, that since I felt I was a superb chemist, I would much rather work on the reserpine metabolism problem because that was chemistry, and his response was, “Well, your chemistry is so good, so thorough, you’re so well schooled that I’m going to offer you a job starting July 1st to work with Steve Mayer on the blood brain barrier”.

LH: That was it.

RM: And, I started to say, “But I don’t know anything about the blood brain barrier, I’m a chemist.” He said, “That’s right, and Steve Mayer doesn’t know anything about chemistry, you should make a perfect team”. That was the way, he worked.

LH: There was some logic to that.

RM: I worked for this man for 10 years. I knew him until his death. He always called me Mikel. I don’t know where he got that pronunciation from. In July, I started working with Steve Mayer, did my Master’s on the blood brain barrier. Steve taught me anatomy by the Braille system, literally. The following year I got married, came back to Washington with my wife..

The second night we were there, I called her up at three in the afternoon and said, "I'll see you tomorrow morning, Dear, we're doing a 24-hour overnight dog infusion, and we will spend all night with a dog".

LH: That was Brodie's style, too, wasn't it?

RM: That was Brodie's style. And, so I spent two years, did my Master's on the blood brain barrier, and my first publication ever in *JPET*. And, then I stayed on, looking at, what are now called, P-450 cytochrome systems.

LH: Who were the people there in the lab at the time?

RM: When I first came there as a graduate student, Julie Axelrod had just finished his PhD for Brodie. In fact, Julie served as one of the examiners on my Master's committee. Sid Udenfriend was Brodie's Deputy Lab Chief. Down in one end of the 7th floor north corridor was a large lab with a young post-doc named Parkhurst Shore, who was working on serotonin and norepinephrine, which I never heard of. In that lab with Parkhurst Shore were two visiting scientists, one from Switzerland, named Alfred Pletscher, and one from Gothenburg, Sweden, named Arvid Carlsson.

LH: Arvid Carlsson. God, what a bunch of giants!

RM: Yes, yes. The section heads included Bert Ladue, who went on eventually to Michigan.

LH: He went on and made his career in drug metabolism.

RM: That's right. Udenfriend had a section. There was a guy who went on to become eventually the head of the department at cardiovascular pharmacology at Emory. And, the grad students were Ronnie Kuntzman and I. That was an unbelievable lab. I learned more pharmacology going down to lunch in the Building #10 cafeteria on the 7th or 8th floor, and sitting around the table of 8 or 10, than a student today can learn in a year of classes. I mean, we lived, ate and breathed pharmacology, chemical pharmacology. It's interesting. When I talked later on with Ronnie, we agreed that the reason that all of us were so close, because we all felt at least once or twice a month, like opening the window in Brodie's office, taking him by the throat and hanging him out the window.

LH: Apparently, he could be damn annoying.

RM: You know what his nickname was, Steve.

LH: Oh, yes, Steve.

RM: Now, you know where that came from. Steve Brodie was the guy who jumped off the Brooklyn Bridge and survived. First of all, he never came in at 8:30 in the morning. He never showed up before 10, 11, or noon. And then he'd work on until the wee hours of the morning. He'd come into your office at about 4:30, when you're getting ready to go home because you've got class that night and your wife has got something cooking in the apartment. I lived in Washington close to Georgetown where I went to

grad school, had classes at night, and he'd say, "Let's take a flyer". And oh, man!

LH: That meant another long night?

RM: That meant an off the wall experiment that had, at first glance, no reason; whatsoever, to succeed, but, then I'd say 85% of them worked. The man had the ability to elicit creativity from his people, and we were his people. There's no question about that. People said, and you'll hear this from a number of people, that he stole ideas and pirated ideas from his people and he presented them as his. Yes, he may have, but he also stimulated your brain to just explode with ideas. He had a talent that I've never seen since.

LH: Yes, he could come up with more interesting ideas in five minutes than most people could come up with in days.

RM: But, anyhow, that was the way it all started and we kind of also had the advantage of having an almost unbelievable nest of people around him. For example, I had, and I say this literally, I had the privilege of being one of the people who first used the very first Bowman.

LH: The first Bowman?

RM: Before he even made one.

LH: Oh, that was when Bowman did his own handcraft,

RM: Yes, and you looked into it as it would be a telescope.....

LH: Like a surveyor.

RM: Right, that you looked into, and you couldn't touch it with your eye because you'd get a shock. The whole thing wasn't grounded well. But, we had that instrument and we could use it.

LH: Well, Bowman's specrophotofluorimeter was a revolutionary tool.

RM: I stayed on 5 years after I finished my PhD, and a post-doc. Another story that tells how Brodie was: He had a young visiting professor from England, named Mike Bevin. He's either still at the NIH or he's retired, I'm not sure. Mike was a pharmacy graduate from Chelsea College of Science and Technology and was assigned to me to do some collaborative work. Brodie came in one day, again one of these 4:30 visits in the afternoon when we wanted to go home, but since he only started at noon, for him the day was just half over. So Brodie came in one day and said, "I've got a problem," and holds up a sheet of paper. He'd just gotten a price quote, now this would have been about 1961, I'd say, roughly, and he had a price quote of about eight thousand dollars from New England Nuclear for either D or L titiated norepinephrine. and, he said, "I can't, I don't want to spend that much money".

LH: Make it.

RM: No, no, that would have been easy. He said, "There has got to be a way to find out when you give DL-norepinepherine to an animal, which of the

isomers is taken up into tissue and which ones are rejected". He said, and he looks at the two of us, and says, "You're a chemist, you're a pharmacist, go to the literature, and find out a way to do this". So, we did; we went to the literature and we talked it over and we came up with a real weird idea that would have been really taking a leap. And, when we went to Brodie he said, "Sure, go ahead but I tell you, I don't think you guys can do it". He said, "I will bet you each a good bottle of imported French champagne, that you can't do it".

LH: That's a good motivator.

RM: To make a long story short, we did it. We got three publications and a bottle of French champagne each.

LH: He could use everything, from bribes to charm.

RM: Right, right, any way he wanted. And, we could always tell where Brodie traveled, from the visiting scientists who came two years later. We had the year of the Italian visiting scientist, the year of the French, the year of the German, the year of the Japanese.

LH: They all followed.

RM: Two years later, the visiting scientist would be here.

LH: The pied piper of pharmacology.

RM: And, then, he got into bringing in these visiting scientists; it was unbelievable. I had one from Germany, who has since passed away, named Eric Westermann. Eric had worked for Schmiedeberg's Laboratory.

LH: That's the father of chemistry.

RM: Right, right. And, Eric had been a young lad at the tail end of the Second World War when Germany was in deep trouble, and so as a 17 and a half year old, Eric had been recruited into the German Navy and they trained him to be a submariner on a U-boat. Okay, not unreasonable, right? One slight problem, Eric Westermann was 6 foot 3 inches.

LH: So, he couldn't fit?

RM: He had a permanent scar right in the middle of his forehead from where he had walked into the hatchways that are only so tall, permanent scar right here.

LH: Some people have dueling scars, scars from a Heidelberg retreat, he had a U-boat scar.

RM: But, that was again typical. Brodie would bring people in and throw them, literally, to the wolves, put them on a problem that they had no reason to be on, but he challenged you. He challenged you to dig into it, to develop it, to do it. And, he was also very much a professional. And, he firmly believed in organizations like the College, and he firmly believed that his people should follow, if you will, in his footsteps and become members and be active and do things. And, that was another way. We'd go out

to meetings and I can remember one meeting where we were standing at a social gathering like tonight's reception, and someone came walking up to us, who did not definitely know that we were all from the same lab, because we had on our name tags in addition to our name only Bethesda, Maryland, and said to one of us, to Gertrude Quinn, in fact, "You know, you people from Brodie's lab, you're a cocky bunch!" And, the two of us that were there, and Gertrude said, "You bet we are!"

LH: So, he really created a team spirit.

RM: He did, he did. There's no question about it. If I had a question about something, his idea was, to talk about it to anybody else in my laboratory or go talk to him. Going outside was fine, but start with the people in the laboratory, and if you want to collaborate on a problem with some one outside it was also fine. You need supplies, or whatever and the budget right now won't handle it, come see me. Finally, I got my PhD in 1960.

LH: From where?

RM: Georgetown.

LH: Almost the same way as Julie did.

RM: Yes, yes, going to school at night. In fact, my PhD thesis committee was on the P-450 liver microsomal drug enzymes across species.

LH: So, it was in biochemistry?

RM: No, it was in biochemical pharmacology. But, my thesis committee, in addition to the one member from Georgetown, was from the chemistry department where I actually took my courses. And Brodie was there, he was on the committee. The three other members were Sid Udenfriend, Paul K. Smith, who was chair of the department at George Washington, and Theodore Caponti, who was chair of the department at Georgetown.

LH: Boy, that's a tough committee.

RM: My thesis defense was at 9 o'clock in the morning at Georgetown, at the University. And, of course, breakfast at such an exam is a cup of coffee; you're too nervous to eat. I went down to the exam and it was over at quarter of twelve. They took me to Billy Martin's Carriage House in Georgetown for lunch. And, the first thing they plunked in front of me was a double martini.

LH: Well, they appreciated what you needed.

RM: Right, right. Sid Udenfriend is driving me back to the NIH after it was all over turns to me and says, "You know, Roger, I hope you didn't think that we were trying to be nasty or anything. That was just a typical PhD oral defense". I didn't really care by that point in time.

LH: Is Sid still alive?

RM: I believe so. Yes, the last I heard he was retired, but I think he's alive.

- LH: Now, we really ought to get him on this history thing. I think he's living in the New York area.
- RM: Yes. I think he is, yes. I don't know about John Burns.
- LH: Burns?
- RM: Who replaced him as Deputy Chief in Brodie's lab..
- LH: I'm pretty sure John is still alive.
- RM: I've seen John about a year ago. But, now that was typical Brodie doing. Anyhow when I got my degree I didn't know whether I wanted to stay around or not. I had done the blood brain barrier work; I had done the drug metabolism work; I had some publications. And, I got a couple of feelers, one was from Brookhaven National Labs; they were looking for biochemical pharmacologists; they were doing some government work. I had one or two other post-doc positions, and I was then making about \$6,000 a year at the NIH; this was 1960. In fact, I can tell you exactly, I was making \$6,345 per annum before taxes or anything. And, these post-doc positions were offering about \$8,500. Well, a \$2,200 pay raise is, you know, with a wife and one child, looked pretty attractive, especially in those days. So, I went in to see Brodie and said, "You know, basically I wouldn't mind staying here, but gee, you know, I'm a GS-7". I would have been eligible in October to go to a GS-9, which would have been about \$800 pay raise. He said, "Well, let me see what I can do. I've got some projects I would love to have you work on". That was just about the time that Westerman had come and we were starting to work on reserpine, stress, pituitary adrenal control, biogenic amines. And, he also said, "Don't do anything until Monday". This was a Friday about 2 o'clock in the afternoon. I said, "Okay, but I've got to tell, one of the people who gave me a deadline the following week". So Saturday at about, right after lunch I got a phone call. It's Brodie. He said, "I want you to be in the Associate Director's office Monday morning at 8:30". And that was Bob Berliner. He was then Associate Director for the Intramural Program of the Heart Institute. I showed up there and Berliner's Administrative Assistant, Evelyn Adox, who has also since retired, said to me, "Steve talked to me at a cocktail party Friday night and he talked to Bob at the same cocktail party. He wanted me to show you this and ask you if this would be satisfactory". And, she shows me an appointment as a GS-11, a double jump from a 7 to 11 instead of 7 to 9, at a salary of just around \$8,000 or \$8,200, something like that. I said, "Yes," and she said, "Good," and pulls out another piece of paper and says, "Here, sign this". I said, "What am I signing?" She says, "Your resignation letter". I said, "Huh," and she said, "You're resigning as of 8:30 this morning so we can rehire you as a GS-11 as of Monday morning".

LH: Therefore, they won't be trapped in by Civil Service. My God, he can work every angle.

RM: He worked that angle out at a cocktail party. So, I stayed on for five more years.

LH: How many people did he have that kind of relationship with?

RM: I think the whole NIH. I'll give you another example. He wanted someone to work with Harriet Mailing who was starting to get into hepatotoxicity, and alcoholism. And, he didn't have anybody in the lab who knew anything about reading liver pathology, histopathology. So, he called me in one morning and said, "You're going to spend the next two weeks over in Building #204". And, I said, "What am I doing over there?" He said, "Ben Hyman", who was one of the best known animal pathologists in the country, "is going to teach you all about liver slides". So, I spent two weeks in Hyman's lab, literally sitting and looking at hundreds of liver sections to learn how to differentiate between pre-cirrhosis, cirrhosis, just fatty liver, and then came back. And, he did that over and over again. Around the same time, or just shortly after that, Parkhurst Shore, who had been Brodie's specialist, if you will, in radioisotopes, because ^{14}C and Trillium were just becoming available at that time in the early 60's, had announced that he was leaving to go down to the University of Texas, Southwestern Medical School in Dallas. And, Brodie called me in one day and he says, "What do you know about radioisotopes?" I said, "Oh, I had a course in undergrad school and a course in graduate school". He said, "Good, that's perfect". I said, "What's perfect?" He says, "You're going to become my lab's Radioisotope Safety Officer". I said, "That's great. I don't know that much about it". He said, "Oh yes, that's alright. Your kid isn't in school yet, is she?" Our little daughter was then about five. I said, "no". He said, "Good, you and your wife have a six weeks vacation in Oak Ridge, Tennessee". I said, "Vacation?" "Yes, sending you down to Oak Ridge Institute for Nuclear Studies for a six weeks training program".

LH: Oh, gee! How could he work so many angles?

RM: I don't know. I really don't know, Leo. This guy knew more people in more places than anyone I've ever known since and could talk things through and get things done, just like that.

LH: You may not want to talk about this, but I remember that Julie Axelrod said the best thing that ever happened to him was to hook up with Brodie, and the next best thing was to break up with him.

RM: Exactly. Julie also used to say, "The good news is the bad news. Good news was, I met him; the bad news was I met him". One thing he did do: he worked your butt off, no question, if he found out that you could do

things for him. I got calls at 11 o'clock at night to come over, we'll work on a paper, and worked at his apartment till 3 or 4 in the morning. I had experiments that would start at 9 the next morning. Tough luck! I got 3 hours of sleep. He came in at noon. It made no difference whether it was Easter Sunday or whatever, if he wanted you, you went. But, at the same time, once he got to know you and knew that he could depend you, he threw you into all sorts of situations that made you come up looking like a piece of gold. I can give you a couple more examples, if we've got time. I had done my thesis work on drug metabolism on lower animals. One of the things I had gotten involved with was conjugation of phenols by fish and amphibians; there's some defects in their systems. Fish don't have the glutathione S-transferase enzyme. So, all of a sudden I get a phone call on Friday afternoon at the office from Brodie, "Mikel, what are you doing this weekend?" I said, "I'm just studying for my oral thesis defense". "No, you can put that off; do that next weekend. Go see Mrs. Ballier". That was his secretary. And he says, "I'm supposed to go to the Dow headquarters in Midland, Michigan on Monday for a meeting to talk about your work. She'll change the tickets; can you go?" Okay, I figured it's my work. He didn't tell my anything about what was going on. So, this was when one of the airlines was on strike, so I could fly from Washington DC to Detroit, but then to get from Detroit to Midland, Dow was going to arrange everything with Brodie. Okay. I packed my bag and told my wife, "I'm leaving you Sunday". "Oh, great," she said. I get a Sunday afternoon flight non-stop from Washington to Detroit. I get off the plane in Detroit and here's a liveried chauffeur with a sign with my name on it saying, "Come this way, Dr. Mikel".

LH: He was mispronouncing it.

RM: Yes. Gets me in the limousine, and drives me over to the Willow Run Airport, Detroit. There's the Dow president's plane, an old DC-3, with chairs more comfortable than on regular planes. We fly to Midland; they put me up in their hotel. The next morning I go to the meeting expecting I'm going to present a seminar to a group of Dow people. No, no. It's a table like this, a little smaller. There is the head of toxicology at Dow, the head of chemistry at Dow, Vernon Applegate, who was the Midwest Associate Director of the Bureau of Fisheries for the US Department of the Interior, the head of the Great Lakes Commission for the US. and Canada, and that type of audience. And, here I am, the scientist, who's going to talk about phenol conjugation problems because they were developing the selective sea lampricides for the Great Lakes. That's what he did, I mean, he didn't care where he shoved you, if he felt it would be useful.

LH: It was sort of sink or swim with him?

RM: Yes, yes, it really was. And, looking back on it, Leo, I learned more in ten years in that lab than most people learn in a lifetime.

LH: And you probably more than once thought of hanging him off the window.

RM: Exactly, exactly. Because, I mean, that was the guy's way of doing things.

LH: Well, I suppose with all of his major contributions you have to think of him as a sort of the Father of biochemical pharmacology. He was a good bet for a Nobel. I remember when I, R. K. Richards, a pharmacologist, came up to me and said, "Guess who won the Nobel prize," and I said, "Well, Southerland, Von Euler and Brodie". He said, "No, it was Axelrod". I said, "Oh God, I'll bet it broke his heart".

RM: I think it may have, but on the other hand I think the reason he never got a Nobel was because he antagonized too many people. I really think that was the reason.

LH: That may have been. You know you don't think of personal things like that entering into a big scientific . . .

RM: I worked on two of his Nobel nominations; he was nominated, at least twice that I know of.

LH: Oh, I'm sure he was. You know it's very simple, one page . . .

RM: Not the supporting documents. It's like an IND.

LH: The original nomination is just one page.

RM: I worked on it twice; to get the documentation together. He had this ability to stimulate you to do your best work, whether you liked to do it or not. He had that talent, that skill. I can remember when he was offered the position of Chair of the Department of Pharmacology at the University of Wisconsin Medical School. This was probably in the mid-1960s, and he was going to take four of us with him. And, he came back from Wisconsin with their whole departmental lists of people and equipment, rooms. Now, you're talking about Wisconsin Med School, the Department of Pharmacology was a big unit, because they taught pharmacy, they taught medicine, they taught nursing. He came back with this tremendous pile of documents. He called the four of us in and he said, "You guys are not leaving this room. I'm bringing in lunch, you can go home for dinner and sleep tonight, but you're coming back tomorrow". Then, he said, "by Friday afternoon," and this was Thursday morning, "I want to know everything that needs to be done if I'm going to make that move". Mimo Costa was another one of the people involved in it. I can't remember who the others were. We worked our tails off but figured out that this is the space we need, this is the equipment, we need, these are the people who can do this, these are the people who can teach that, these are the positions you are going to have to fill. And, close to signing he and Ann,

his wife, went to Madison, and got stuck there in a blizzard. And that was it! Ann said, "No way!"

LH: Well, that was a blessing for the NIH.

RM: And, all our work went down the tubes. But he brought in people who went out and went into industry; they went into the academic world; they went into the clinical world. He brought Mimo Costa in from Italy, and then Mimo went over to Saint Elizabeths and set up that whole unit over there. Well, actually, Mimo when he came from Italy, went to Harold Himwich's place in Galesburg first.

LH: Oh, he fertilized a lot of places. Well, when did you leave?

RM: I left in 1965, because I had gotten to the point where I felt I couldn't do anything else there. And, I wanted by that time desperately to teach. I had one grad student, Frank Miller, who was doing his Masters and I was looking for an opportunity to get to an academic position. And my old friend Danny Efron, who had been in Brodie's lab as a visiting scientist, when I first met him.....

LH: His is the famous saying, "The international language of science was broken English," which he spoke very well.

RM:was then serving in the extramural side of NIMH and had been involved with a program project grant, a big one, at Indiana University in Bloomington that was headed up by Roger Russell. And, Roger had hired a behavioral psychologist from Roche, who had worked on some of the early behavioral work of benzodiazepines, to do the psychology, and hired a neurochemist to do the chemistry, and they were going to do biochemical correlates of behavior. And, the project was not going well at all because this neurochemist didn't know any pharmacology. Fortunately, her husband got a position elsewhere and so she left. And, then, Dan Efron told Roger Russell, "I have just the person for you. If I can get him out of Brodie's lab he can handle the pharmacology and the biochemistry, both". So, I thought if I take the position that would help Dan out because this program project grant would have been floundering otherwise. And it was a big one for those days because it literally salaried, I believe, the equivalent of 4 or 5 fulltime faculty positions. So, he sent me out there to get an interview. I had never heard of Bloomington or Indiana University before then, but it looked very good. It was an opportunity to go into behavior and psychopharmacology, and I went. And, Brodie didn't like the idea of my leaving but he saw what I was looking for, and it was an academic opportunity and I had wanted that. And, that started my academic career; that was it.

LH: How long did you stay in Indiana? Well, Roger left for Australia.

RM: He left for Australia and I stayed on there. Well, actually my career took an even more devious path. Even though I went out there, I was supposed to have a joint appointment with the pharmacology department at the IU Med School in Indianapolis, because they had a first two years of medicine program, at Bloomington. The head of that department at that time was a guy named Jim Ashmore. And when Ashmore found out that Russell was going to hire me he called me and said, "Do you want to have an appointment as a psychology professor?" I said, "I never really thought about it, Dr. Ashmore". He said, "Make you a deal. You take the position- and I'll give you an appointment as Associate Professor of Pharmacology in my department, but assign you to the Bloomington campus, because we need somebody to help develop the program there". I said, "Okay". So, that got me started in psychopharmacology, full-time.

LH: How long did you stay at IU?

RM: I stayed there 12 years.

LH: Then how did you happen to move up state?

RM: Well, that's another one of these fluky things. The head of the department, of what had been the Department of Pharmacology and Toxicology in the School of Pharmacy at Purdue, had been someone named Tom Mia, and Tom was leaving to become Dean of the School of Pharmacy at UNC in Chapel Hill and that position opened up. And, I had been looking around a little bit because I had moved up to full Professor and, so I was kind of nosing around to see how I can move up and become a Department Chair, Department Head. And, when this thing opened up at Purdue I went up and looked and it seemed to fit real well. So I moved up there and became Head of the Department.

LH: How long have you been there?

RM: I have been there now since 1977; that's 20 years. I stepped down as Chair or Head in 1985, because I just got tired of being an administrator, and wanted to do teaching and research. And, then in 1987, they had some problems with their animal care and use procedures, and I chaired a committee that was supposed to tell the university what was wrong with their system. And, we did and they bought the recommendation that they make the Chair of the Animal Care and Use Committee, a half-time salaried position, and I became permanent Chair of PACUC, Purdue Animal Care and Use Committee, and Director of the Laboratory Animal Program, half-time, while keeping my position. So, right now, I've really got three titles: Director of the Laboratory Animal Program and Chair of the PACUC, Professor of Pharmacology and Toxicology in the School of Pharmacy, and Adjunct Professor of Pharmacology and Toxicology, Indiana University School of Medicine.

LH: That's a quadruple there...

RM: I teach nursing students, pharmacy students, medical students, and graduate students.

LH: If you had the right school affiliations, you could have been in a veterinarian school.

RM: Yes, I could have done that, too. But, this all goes back, in a sense, to Brodie's training, because his training of people emphasized, "Don't be afraid of going into something new. If you are truly a trained and capable professional, you can do it".

LH: That's a good philosophy, and it also fosters the idea of life long learning.

RM: Yes.

LH: Of never stopping.

RM: Yes, you never stop. Monday is ACNP's teaching day. I love the College's teaching days, because I teach psychotherapeutic agents to the med students in our small med program. That was about as good an overview of molecular biology oriented towards mental disease and psychotherapeutic agents as I think you could find anywhere. I mean, that just gave me tons of material just sitting there listening.

LH: Well, that's one of the interesting things about the College that it brings so many different fields together and you always have something to learn.

RM: Exactly, and very comfortably, because you don't have any pressure here. You can talk to people from industry, from the academic world, research institutes all over the world and there is no pressure. The only pressure is to learn.

LH: Well, with a little luck you will learn other new tricks, for sure. You're far from finished.

RM: Oh, yes, I intend to keep going. I do have to throw out one more thing because this is another little Brodie anecdote that's cute. In the olden days, so to speak, the Federation meetings and the ASPET meetings were in Atlantic City, or wherever, and Brodie was kind of the undeclared King of having papers there, because you know you had 30 people in this lab, so he'd have 15 or 20 papers at a meeting. But, since maybe one-third of those 30 people were members of ASPET, he would co-author or sponsor 10 or 12. In 1973, I was at Indiana University in Bloomington. I had four other faculty members in the unit, one of whom was an ASPET member; the other three were not. We had 12 graduate students, couple of technicians and the one ASPET member who was there didn't have anything for that meeting. It was at Michigan State, so I either sponsored or co-authored every one of 17 abstracts. I saw Brodie at the meeting and he looked at me and he said, "Mikel, you did it, didn't you?" He said, "You've more abstracts at this meeting than I ever had in my whole

career”. I said, “Yeah, I guess I do”. He said, “See that you keep that record”.

LH: Oh, golly!

RM: That was Brodie.

LH: Your story about the old man is just simply wonderful. That’s exactly what I wanted you to do.

RM: Good.

LH: Because, alas, we don’t have him to tell his own stories and we have to go second hand by first hand witnesses like yourself. And I can’t think of anybody better to give us a feel in what it was like to be a Brodie inheritant. By the way, did they ever tape that meeting with Brodie a few years ago?

RM: I don’t think they taped it. They made a book out of it. I take that back. There is a videotape.

LH: That would be interesting for history.

RM: Yes, and the guys from whom one could access it, are both ACNP Fellows: Ron Kuntzman and Lew Limburger. I think I’ve got a copy, but I’m not sure whether I have it any more, because I’ve loaned it out a couple of times.

LH: It would be nice to have that tape, because he was still pretty functional when it was made. .If we dig far enough, we’ll get some more history. Well, anyway, Roger, I greatly appreciate you spending the time with us...

RM: Thank you.

LH:because, I knew you were going to be able to give us a lot of information and you certainly have.

RM: Thank you, Leo. And, as I say, Brodie was so much a part of my career that I once sat down and tried to figure out how much it would be worth in tuition or time and there’s no way to calculate it. He was a guy who was just unique in his ability to challenge the mind.

LH: A six week vacation.

RM: Yeah, that’s all.

LH: Thank you again, Roger.

RM: Thank you, Leo.

ARNOLD J. MANDELL

Interviewed by David Healy
Las Croabas, Puerto Rico, December 13, 1998

DH: My name is David Healy and today is the 13th of December 1998. I'm interviewing Arnold Mandell,* today, on behalf of ACNP. Arnold was one of the early pioneers in the field, a man of fun and genius, but unconventional genius, I think. Arnold, can we begin with how you came into the field? Well, let's go back to where you were born and brought up.

AM: I was born in Chicago. My mother was a Chicago Conservatory pianist and piano teacher and my father was saxophone and clarinet playing jazz musician and band leader. My mother taught me and pushed me to study classical music. My father used records and stories to interest me in jazz. He had hung around in the Chicago jazz crowd with pioneer, Earl Hines, "the father," and his crowd, which sometimes included Ellington, and had written a piano book with him. So, my childhood was dominated by a tug-of-war between classical music and jazz. As an adult, a similar struggle dominated my work; between psychoanalysis and brain biology.

As I was growing up, practicing three to four hours a day, it was seen as virtuous to work at Bach's Two and Three Part Inventions, and "dirty" to improvise around "I Got Rhythm". I remember writing an arrangement entitled "How High the Moonlight Sonata", which my mother hated. In my early teens and then on, I settled on a piano style that was most like that of Oscar Peterson and tried, but failed, to be Charlie Parker on the saxophone. I, however, did win several American Federation of Musicians contests on classical music for the alto sax.

I have always heard patient's stream of associations like jazz improvisation, with the person's character revealed in the style of their flow of talk. Schizophrenic discontinuity and thought disorder "swing" like Thelonious Monk. Then, there was the plaintive obsessive ruminations of Bill Evans; the manic flight of Art Tatum; the psychopathy of Bud Powell. In 1997, I gave an invited address at the Fourth Experimental Chaos Conference, in which Karen Selz and I used dynamical systems' ergodic theory to quantitatively differentiate between nonlinear measures of a variety of modern jazz styles, as well as early versus late Beethoven. The styles were clearly and quantitatively discriminable.

I got interested more directly in the brain in my early teens when my dad gave me a book from the early 1900s by Roger Blatchford, called *Not Guilty*. It concerned the social psychology of criminality. It developed the

* Arnold J. Mandell was born in Chicago, Illinois in 1934.

position that most people weren't voluntarily evil, but, rather, their style of behaviour was the result of the interaction of the genetics of their brain and the influence of their environment during growth and development. About the same time, he also gave me an early 1930s book on physiological psychology of the brain. It was a very primitive book that discussed among other things, the shapes and bumps in the head in relationship to a person's immutable behavioural patterns.

DH: A point of view that's old, but lost now, isn't it, the notion of the influence of physical constitution?

AM: Well, on one hand it's lost and on the other hand, the same set of assumptions underlies much of our current theories of genetic inevitability; somatotype has been transformed into nucleotide sequences and proteomic expression with the same "anatomy as destiny" kind of finality. When I went to Stanford, having been a brain groupie during my teens, I was really disappointed to find that there were no laboratories of neuroscience or neuropharmacology.

DH: Nothing. You actually went to Stanford in 1958?

AM: No, I was seventeen and entered Stanford in 1951. I majored in psychology and chemistry, and spent my extra-curricular time running rats for professors in Stanford's psychology department, especially for D.H. Lawrence, and working on the unfolding of neural crest tissue to become autonomic ganglia in the embryology laboratory of Graham Dushane. He was very scholarly and quite influential in my life, somehow teaching me the transcendent feeling of the doing of research. He was editor of *Science* for several years.

I was encouraged to frame the rat data so I was getting in the language of mathematical learning theory of the sort being talked about by Sid Siegel, the nonparametric statistical whiz, and Richard Atkinson, later Chancellor of UCSD in La Jolla, and then all campuses at University of California. I was remarkably lucky to have close relationships with these men and other senior post-docs and junior faculty in psychology at Stanford.

I got to be present and participate in discussions late into the night in front of blackboards borrowing chemical kinetic equations to represent learning functions, comparing the drive reduction theories of Hull and Spence with the operant theories of B.F. Skinner and his followers. I also continued to maintain my interest in the anatomy and physiology of the brain for which I was frequently teased by these radical behaviourists.

I also had a memorable semester in a private tutorial with Albert Bandura, reading Otto Fenichel's *The Psychoanalytic Theory of Neurosis*. In my third and final year at Stanford, John Eccles's *The Neurophysiological Basis of Mind* came out, which made learning functions neuroanatomical

and observable even in the spinal cord. I carried the books of Eccles and Fenichel around for years. Maybe it should be noted, relative to my later life, I also fell in love with and took courses in organic chemical reaction mechanisms. I guess I was trying to find some kind of harmony in the aggregate of mathematical, psychoanalytic, neuroscientific and organic chemical thinking. This search for accord became the signature of my inner life, but was already in place in primitive form at Stanford in 1951 and 52. It was also the framework for a lifelong conflict that remains unresolved.

DH: Conflict?

AM: Well, let me begin by saying that I spent close to ten years as a patient, called "candidate," in four times per week psychoanalysis. My first psychoanalyst, when I was at Tulane Medical School in New Orleans, was the New Orleans Institute training psychoanalyst, Irwin Marcus. Later, during my residency at the Neuropsychiatric Institute at UCLA, I entered training psychoanalysis in the Southern California Psychoanalytic Institute, and spent five years with Judd Marmor.

During my first psychoanalysis, in New Orleans, I worked nights and weekends doing spinal cord research in cats under oil in the Physiology Department directed by Matt Bach, an early student of Horace Magoun, of reticular formation fame. The work itself was inspired in part by John Eccles and in part by Horace Magoun, especially the 1951 symposium, *Brain Mechanisms and Consciousness*, edited by Jasper.

I also spent a couple of years around Robert Heath and his group watching him use depth electrodes in the human septal region for stimulation in schizophrenics. He focused on the inability of chronic schizophrenic to experience pleasure: anhedonia. Septal stimulation was found to be pleasurable to these patients. They were outfitted with stimulus boxes on their belts so they could dose themselves as needed. Heath's group also was extracting plasma from schizophrenics looking for what he believed to be a unique protein fraction, something he called taraxein.

Heath was the reason I had gone to Tulane in the first place. He had promised me a place in his laboratory. He looked like Gary Cooper, and his charisma and easy familiarity with both brain biology and psychoanalysis were really seductive. His background participating in the Columbia-Graystone Project, involving selective cortical and limbic ablations in chronic schizophrenic patients as well as his psychoanalytic training under Sandor Rado made him a living representative of my fondest dreams for myself. Nonetheless, I found his laboratories too intimidating once I got there, so after a year or so, I switched to the uptown physiology department, under the supervision of L.M.N. Bach.

I published my first scientific paper in 1956, comparing brain stem descending and local spinal cord inhibition and their interaction in the lumbar spinal cord in the anesthetized cat. My second paper, delivered at the Fall Meeting of the American Physiological Society of that year, reported a relationship between medial bulbar sites eliciting descending motor inhibition under anesthesia and the same site in the awake cat generating fear behaviour, and lateral bulbar sites eliciting motor facilitation under anesthesia and out of anesthesia, pleasure, indicated by languorous purring.

In those days there was a great deal of tension between “biological psychiatry” and “dynamic or psychoanalytic psychiatry”. My fellow psychoanalytic candidates and some of the teaching analysts told me directly that I couldn’t be a real psychoanalyst and a biological brain researcher at the same time; that I had to choose. It would be considered silliness now but it was an issue full of rancor in those days. Biological Psychiatry was considered a “resistance” to psychoanalytic insight by many. The issue came to crisis during my psychiatric residency at UCLA’s Neuropsychiatric Institute.

DH: What happened?

AM: I was in the same conflictual position again. On one hand, I was getting analyzed four times per week with Judd Marmor, and spending four hours a week in Southern California Psychoanalytic Institute seminars. On the other hand, the Brain Research Institute space committee gave me the laboratory that had belonged to the psychopharmacology pioneers, Eva and Keith Killam, who had transferred from UCLA to UC, Davis.

From seed money and some NIH and State Mental Health Funds, I developed a biochemistry laboratory that studied the interactions of human limbic stimulation with corticoid release and plasma levels. We collected several times per week and several times per day, urinary corticoids and tryptophan metabolites in bipolar patients, and, studied the effects of elevated plasma and urine corticoids on tryptophan metabolism in man. Following some early animal work on hepatic enzyme induction with corticoids by Knox and his group at Harvard, my team, particularly Irene Mersol Sabbot and Robert Rubin and the clinical staff of my Neuropsychiatric Institute in-patient unit, collected urine every six hours for weeks in urinary time series in starving patients and in patients with disordered affect.

We published several papers reporting our story, principally about the metabolic evidence of the induction of hepatic tryptophan pyrolase activity in depression associated with elevated urinary corticoid excretion, and the cleavage of the indole ring leading to marked reduction in peripheral serotonin metabolites, one of which I reported in man for the first time.

I got the Society for Biological Psychiatry's A.E. Bennett Prize for this work. This finding was indirect evidence of a possible brain serotonin deficiency in affective disorder. Ed Sachar, at Einstein, and Biff Bunney, at NIMH, were also following steroids in affective disorder found a peak in depression.

My fellow analytic candidates in Southern California at the time called me "the urine boiler". They teased me about trying to understand the human soul through the kidney. I just didn't want any more of what was sounding more and more like a fundamentalist religion. I finished my training analysis with Marmor, who was supportive of my biological research life, treated two training clinic patients classically analytically under supervision - three were required for institute membership - and attended analytic seminars for five years. One day I decided I had had enough.

When I resigned from the Institute, several of my candidate and analyst friends told me that no one would believe that I had resigned. They insisted that everybody would assume that I had been thrown out. That fixed it for sure. I was finished. Beyond what I had done, it seemed a waste of time. It got less and less relevant to my clinical interests, and I was finding the brain relevant research increasingly exciting. I wanted to chase the serotonin story into the brain. In addition, around that time, I had several critical clinical incidents that led me into psychopharmacology.

DH: What were the incidents?

AM: I guess the issue can be captured in two stories. The first story was during my residency when I was doing several months of daily psychotherapy with an in-patient. She suffered from what was known in those days as "involuntal depression", which rode on an obsessive-compulsive, passive-aggressive character. She was getting worse and worse every day. Although the supervisor recommended shock treatment, I was in analysis and in psychoanalytic seminars and wanted to see what I could do with insight. They agreed to let me keep her in the NPI hospital for months to try. The patient was the unmarried older sister of a bookkeeper. She was the caretaker of her aging mother, and in her early fifties she began to lose sleep and weight, experienced a marked increase in her obsessive-compulsive traits and became suicidal.

My psychotherapy was about her unconscious frustration and rage; her resentment of her sister, and mother, for stealing her life from her. This treatment appeared to be making things more painful for her. She, of course, felt accused, but denied it all and the talk only made things much worse. All the while she continued her passive aggressive praise of me for making her so much better. I was growing desperate because I didn't want to use ECT, but saw it as inevitable.

It was at this time, in 1960 that I got a drug from a detail man, a new Ciba-Geigy drug, imipramine-Tofranil. It was initially thought to be antipsychotic, but was showing antidepressant actions. I will never forget the third day of her treatment with imipramine. I was late for the daily visit, and when I entered her room, she looked at me with obvious irritation, for the first time, and said, "You're late". She had never been able to speak to me, or I think almost to anyone, like that. In the next three weeks, her syndrome of over two year's duration disappeared! Her sleep and appetite returned; her delusions of "smelling bad" and "contaminating the chairs if I sit down" were gone. She was easily able to speak about her "boxed in" state and began to make new life plans for herself.

From a dynamical point of view, imipramine reduced her separation anxiety - Don Klein developed this thinking most clearly - which trapped and unconsciously enraged her; her felt anger made her feel like a "bad person". She described how happy she was with her new "freedom to choose". That was my neuropsychopharmacological moment! I saw that not only symptoms but permanent characterological features of a person could be changed with these new psychopharmacological agents. Who a person was could be altered; not tranquilized, not muted, not speeded, but changed in fundamental ways such that the "new person" was not capable of manifesting the presenting illness.

It was about this time that I began a long lasting and close relationship with Nathan Kline, known for his pioneer work with reserpine and monoamine oxidase inhibitors. Nate's real greatness was in the intimate observations he made on the patients he was treating with drugs. When we talked, it was inevitably about how the drug influenced subtle aspects of the whole person, his fantasy life, his sexuality, ambition, aesthetic tastes and appetites, and subtle aspects of the therapist-patient interaction.

Our relationship lasted until his death in the late 1970's. Nate was known as a wild, drug wielding, cowboy. What most people didn't know about Nate was his subtle, highly personal, psychodynamic view of psychotropic drug actions. He saw his drug treatment patients over significant amounts of time using long term follow-ups.

People came from all over the Country to see him. He was a marked influence on how I practiced psychiatry. When I would notice a drug induced change in a person, even not relevant to his presenting disorder, say lithium reducing the obsessive urges to gamble or binge drink, I would call and talk to him about it. We spoke about lithium "slowing down" internal processes sufficiently to allow good judgement to play a role in its effect. I always took him seriously, even literally, and he was usually right. For instance, I studied lithium effects on brain enzyme kinetics, and

made some computations concerning measures of diffusion in lithium-structured water; all of it pointed to a “slowing” as a global phenomenon.

For the rest of my professional life, I thought of effective psychopharmacological treatment as changing a person into someone else who was less vulnerable or even incapable of having the psychiatric disorder with which they had originally presented. I saw, and see, drugs as altering the defense pattern and strength of the person, and that this, secondarily, becomes therapeutic with respect to the patient’s diagnosis. There must be a psychobiology of character and its changes.

During my stay at UCLA in the early and middle 1960’s every patient got an MMPI and therefore a characterological profile. I watched drug treatment change the “shape” of the MMPI profile, particularly in the Axis II characterological scales. Tricyclics reduced or eliminated the MMPI profile of a ruminator. Low doses of antipsychotic changed the Sc-Pd MMPI profile, called, but not really, “schizoid-psychopathic” character. Anti-epileptics changed the threshold of the hysteroid-impulsive ego disruption of the Hy and Hs (hypochondriasis) parameters. Acute changes in anxiety, Pt (psychasthenia) and D (anxiety, depression) were to be expected, but changes in indices of long term character patterns were not. Many wonderful studies by others have since supported this kind of thinking since those early, “pre-scientific” days. Like Chinese medicine, rather than emphasizing DSM-III Axis One catalogued primary symptoms, I was always most aware of the Axes Two dimension, the patient’s character and personality and let these variables play a significant role in drug choice and dose.

This theme found its way into my neurobiological research, as well. Our laboratories focused on long lasting psychotropic drug induced changes in long lived macromolecular reflections, such as the neurotransmitters’ rate limiting biosynthetic enzymes and the sensitivity state of the relevant receptors, as representative of characterological states. These were the changes invoked by chronic administration of antidepressants and antipsychotics in experimental animals, and I viewed these changes as the neurobiological correlates of characterological change.

The second story is more about the state of psychiatry in the early 1960s. I went to my first American Psychiatric Association meeting and also to the meetings of the Society of Biological Psychiatry and of the American Psychoanalytic Association. Once, at a luncheon with the biological psychiatrists, I just happened to be sitting across the table from a very thin, bearded, threatening looking man in his late fifties who described his current research project as doing “ice pick lobotomies” on “acting out adolescents”. This was, as I later learned, my first contact with Walter

Freeman, the major protégé of the Portuguese Nobelist, Antonion Moniz, who invented the lobotomy.

Terrified, I ran across to the Waldorf Hotel where I thought the psychoanalysts were meeting. Breathless, I entered a big meeting hall and found a seat in the corner. Lo and behold, the man in front was speaking Yiddish. Since I knew that there was a heavy Jewish membership in the psychoanalytic societies, I wasn't surprised, at least for a little while. I was sitting there, uncomprehending, for about twenty minutes before I saw a sign in the corner that said B'nai B'rith. It was a meeting of the Jewish advocacy group, not the American Psychoanalytic Association! So that was what a brain groupie was faced with in the late 1950's and early '60s. A choice between lobotomies or a Jewish fellowship!

DH: Were you teaching then?

AM: Yes, as a NIMH Career Teacher Awardee in 1962, I developed the first undergraduate medical school course in clinical psychopharmacology at UCLA. It was a three-week course, taught within the psychiatry block in the third year. For drug indications, their mechanisms and their effects I combined two points of view: neurobiological mechanisms of action that included biogenic amine dynamics, limbic system function etc. the basis for which was taught by Wallace Winters and Charles Spooner in the Pharmacology Department, and a psychoanalytic view of personality and character. Much of the clinical material was from my own Beverly Hills-Brentwood practice, which I maintained for about 40 hours a week with a full Saturday, done after 4:00 PM each day.

It was the early 1960's and I was doing dynamically oriented psychotherapy along with psychopharmacology. I saw each patient one, two, or more full "fifty-minute" hours a week with or without drugs. The current practice, the very short time spent by psychiatrists with patients, using powerful drugs that make major global changes in personality, most of which they are unaware, is upsetting to me. These powerful drugs influence so much of a person's inside and outside reality, and so little of what is being changed is being observed by the psychiatrist. I see it as insurance plan supported very bad practice.

DH: What do you mean by psychopharmacology from a personality dynamics point of view?

AM: I actually talked about it for years and wrote about it for Judd Marmor's recently republished book, called *Modern Psychoanalysis*. I called it "dynamic psychopharmacology". I was talking a lot at that time with Donald Klein, of similar bent, who was studying the relationship between personality type and drug responses. For example, Donald Klein described two different drug responsive anxiety syndromes.

Many others were also working in this area. For example, DiMascio and Gerry Klerman described the poorer response of hyper masculine types to non-motor activity promoting phenothiazines, such as Thorazine, compared with Stelazine (trifluoperazine). Of course, the new antipsychotics, with considerably less extrapyramidal influence mitigate this difference. A “fat and sleepy” depressed person responded better to monoamine oxidase inhibitors, and the “thin sleepless” depressed person was more responsive to the tricyclic agents, such as Tofranil.

I insisted on once, twice or more a week of close clinical, full hour attention to patients on psychopharmacological agents, from my senior residents. This yielded regular discussions of the subtle and global personality properties of the drug response. Mortimer Ostow continued psychoanalysis with patients taking psychotherapeutic agents and spoke of descriptors such as the amount of “extrapyramidal libido”. He spoke of titrating psychic energy using blink rate.

I was convinced that the tricyclics reduced inertia and facilitated action in depressed patients, so I extended the observation. In 1962, I published several papers with evidence that Parkinsonian rigidity and inertia, not tremor, was almost completely mitigated by tricyclic antidepressants. I called it “Motivation and Ability to Move”. The neurosurgeon, Robert Rand, at UCLA said that previously poor prognosis Parkinson patients on tricyclics became good candidates for surgery, having lost their rigidity which was not subject to improvement by pallidectomy. About the same time, I also worked with Rand and Robert Rubin, my students, to show that stimulation of the amygdala in their electrode implanted temporal lobe epileptics increased plasma and urinary corticoids, while hippocampal stimulation reduced plasma and urine levels. In my course for medical students I was speaking of amygdala fear and rage and hippocampal peaceful transcendence.

I commuted to Boston once a year or so to attend Normand Geschwind’s clinic and shared dinner with Harvard’s neurology professor - who should have shared Sperry’s Nobel Prize for his theories of hemispheric “disconnexion” syndrome - and spoke with him about his remarkable collection of temporal lobe syndromes. His transcendent, asexual right lobe syndromes reminded me of St. Paul and some of the phenomena I experienced during the effects of LSD, which I obtained for personal experimentation from Barbara Brown at the Los Angeles VA Hospital. I was immersed in Barbara Meyerhoff’s studies of the Hiuchol Indians who took Peyote with their ritual practices. I was also one of Sacha Shulgin’s human subjects when he was developing the methoxy- and halogenated-amphetamine series, one of which is Ecstasy.

There were seven of us, Sacha Shulgin volunteers, with identities known only to Sacha. We each sent him our notes on our subjective observations after taking the various compounds and doses that he sent to us. I was also involved in some of the Army Chemical Corps conferences on the subject of hallucinogens. I put the phenomenology of all of this together in a 100 page essay developing a “drive-arrest-release” neurobiological theory of transcendence. It was called *God in the Brain*. It was published in *Psychobiology of Consciousness*, edited by Davidson in the mid 1980s. I still get reprint requests for it. James Austin’s book, *Zen and the Brain* used this theory, and some of the experiences were the substrate for my Simon and Shuster Book about phase transitions in man called *Coming of (Middle) Age*.

DH: You said at the beginning of this interview that you began to chase the serotonin story.

AM: While moving from UCLA to UCI in 1965-6, and then after being appointed in 1968-9 Founding Chairman of the Department of Psychiatry at UCSD, in La Jolla, I put together a team to study the neurochemical and animal behavioral correlates not of the initial responses to psychotropic drugs, such as blocking uptake, releasing monoamines, receptor agonistic action, etc., but rather the longer term, what I called adaptive, changes when the animal, rats, was given drugs regularly over days and weeks. Regimes of the sort used in real clinical situations. That “latency to action” was the theme of almost twenty years of work, before I changed my focus to dynamical systems in neuropsychobiology, and my following 18 years of work with Karen Selz and others in the Mathematics Department at FAU, in Boca Raton.

The group at one time or another at UCLA, UCI and UCSD included Drs. Lee Poth, Wallace Winters, Charlie Spooner, David Segal, Mark Geyer, Ron Kuzenski, Suzanne Knapp, Pat Russo, Louise Hsu, Wilson Bullard, and later, Martin Paulus, Steven Gass, Peter Leopold, and others.

Lee Poth was particularly important in organizing and moving my laboratories from UCLA to UCI, and then again to UCSD. I don’t think I could have done it without her. She was not only the one that best articulated what we did in my laboratory. She also was the one who found the tryptamine methylating enzyme in rat and human brain, a fun thing to think about with respect to the brain making its own hallucinogen, DMT. Richard Wyatt explored this possibility extensively. Lee later went on to work with the Nobelist, Julius Axelrod who also, among his many accomplishments, was a very significant contributor to the biogenic amine methylation story.

The twenty plus years of research work, from 1966 to 1982 that followed was about “adaptive regulation”. It was our theory that the brain’s

molecular biological and biochemical adaptation to the perturbation by a drug, not its initial action, was the mechanism of its therapeutic efficacy. Tricyclics acute blocking of uptake in biogenic amine synapses was followed by a long lasting adaptive decrease in the rate limiting enzymes, tryptophan hydroxylase and tyrosine hydroxylase, for the synthesis of serotonin, norepinephrine and dopamine, as well as reduced sensitivity of their receptors. I saw the drug induced, long lasting changes in the biosynthetic and receptor proteins as representative of the chemical “characterological” changes required to successfully defeat the pathophysiology. It was, once again, a way of fitting psychodynamically and neurochemical thinking together.

DH: This kind of talk sounds a lot like Peter Kramer’s, *Listening to Prozac*.

AM: Exactly.

I think we still haven’t psychoanalytically or neurochemically untangled the neurobiological or dynamical-characterological relationship between the loss of sexual libido and the improvement in disposition that often occurs together in people given SSRI’s. Norman Geschwind spoke of the right temporal lobe epileptic change in personality toward a beatific kindness toward everyone and loss of interest in sex.

DH: You had a pretty talented group of co-workers.

AM: I have been very fortunate that way. I was always looking for researchers who would do what they were doing even if they didn’t get paid for it. They made a remarkable series of findings. David Segal was the first to show that intraventricular norepinephrine in rats produced behavioral activation. He also developed an animal model for adaptive regulation, and perhaps bipolar disease, using the chronic drug administration paradigm. He showed that daily administration of reserpine produced gradual decreases in spontaneous motor activity to almost immobility, until day nine at which time that rats within a few hours became suddenly, continuously hyperactive, night and day, for several days. The change happened suddenly, and we wondered whether this was a model of what Biff Bunney called “the switch” into mania from depression in bipolar disease. This work was published in *Science*.

Another yield of the long-term drug strategy was David’s discovery that intermittent administration of amphetamine induced progressive increases in sensitivity, instead of the expected tolerance, to the drug. The supersensitivity lasted months in rats. Several of our abstinent ex-addicts working in the drug treatment program I started, the first methadone maintenance program in San Diego, tested which flavor would be best. It was remarkable that they were drunk for hours from a highly diluted single teaspoon full of methadone that I didn’t even feel.

In the early 1970s in my laboratory David Segal was the first to discover behavioral sensitization to a psychopharmacological agent, and Ron Kuczenski to demonstrate allosteric regulation by a brain enzyme protein. He showed that heparin, chondroitin sulphate and other membrane components activated tyrosine hydroxylase, the rate-limiting enzyme for norepinephrine and dopamine. Among the many other things, Suzanne Knapp discovered that lithium stimulated, and cocaine blocked, the tryptophan uptake path in serotonin nerve endings. Chronic lithium created a serotonergic buffer: increasing serotonin synthesis by increasing tryptophan uptake against a compensatory decrease in the rate-limiting enzyme, tryptophan hydroxylase, reducing serotonin synthesis. The range of variation of brain serotonin was thus constrained below and above into a narrow range. Mogens Schou, who followed John Cade in pioneering lithium use in affective disorders, told me that he liked our serotonin buffer theory, and I was told that he used it in several of his lectures. The principle of this kind of buffer has recently been applied to other synaptic chemicals such as the excitatory glutamate neurotransmitter. I was given the Foundation Prize in psychiatric research by the APA for this work in adaptive regulation and its manifestations in the multiphasic actions of lithium.

Somewhere in this time, we also developed what we called “the NIMH neuron”. Several nonlinear mechanisms were working to modulate the function of biogenic amine synapses at the same time, and we studied them in parallel. For example, with respect to the serotonin neuron, we studied simultaneously tryptophan uptake, tetrahydrobiopterin cofactor generation, allosteric state of the rate limiting enzyme, tryptophan hydroxylase activity, vesicular storage and release mechanisms, cellular synthesis of tryptophan hydroxylase, variable rates of axoplasmic flow of the enzyme, nerve ending release and reuptake of serotonin, presynaptic feedback via autoreceptors, and dependence of postsynaptic action upon the variable sensitivity of multiple serotonin receptors. We studied all of these mechanisms simultaneously, in addition to behavior in response to psychotropic drugs in rats.

DH: What was the relationship between these basic studies and clinical psychopharmacology?

AM: Much of the creative inspiration about psychopharmacology in my teaching to medical students and residents, as well as in my clinical practice came from my annual two week meetings with The Denghausen Group on one or another Caribbean Island. It was like a meeting of gris-gris men of brain drugs.

DH: What was the Denghausen Group?

AM: Beginning in the middle to late 1960's, organized by Nathan Kline and supported by the Denghuasen Foundation, an international group of pioneering psychopharmacologists met every two years for 10 days to 2 weeks to discuss subtle clinical psychopharmacology issues. We each gave informal talks involving our clinical observations or new, usually unpublished, basic research findings. We had, sometimes heated, discussions in the mornings and then had the, afternoons free to enjoy with our significant others. It was a diverse collection of scientists, including two Nobelists. The Denghausen Group included Nathan Kline, known for his work on reserpine, monoamine oxidase inhibitors, lithium for alcoholism; Heinz Lehman, a Canadian pioneer who in his long term collaboration with fellow Canadian, Thomas Ban, both significant pioneers in psychopharmacology, introduced and elucidated the use of phenothiazine antipsychotic treatment in schizophrenia; Floyd Bloom, a world class neuroanatomist studying the physiology of brain stem amine neurons, actions of peptides; Larry Stein, known for self administration and self stimulation in the application of Skinnerian learning models to psychopharmacology; William (Biff) Bunney, a classical pioneer in neurochemical and hormonal studies of affective disorder, head of the clinical research unit at NIMH; Arvid Carlsson, Nobelist discoverer of role of dopamine, its relationship to the actions of antipsychotics and its metabolism among many other things; Philip Berger, an outstanding Stanford psychopharmacologist; Jose Delgado, a Spanish neurosurgeon famous for arresting a bull at a distance with caudate stimulation and of course, fundamental human neurophysiological discoveries; Roger Guillemin, a Nobel Prize winner for his discovery and sequencing of several important neuropeptides; Mogens Schou, responsible for the clinical development of the use of lithium in affect disorder; Jules Angst, an important European psychopharmacologist responsible for many large population psychiatric drug studies; Ed Sachar, an early and important discoverer of the corticosteroid responses in depression and its recovery suggesting that depression "is a hypothalamic disease", and who, in his characteristic humble way, gave me credit for that phrase, but it was his; Julian Mendlewicz, a creative and productive academic Belgian psychiatrist and psychopharmacologist; Alec Coppen an important English psychopharmacologist, who was known for his careful long term drug studies in psychiatric disorders, and me.

I learned very valuable, empirically useful clinical things from the Denghausen group, like the use of low dose lithium to potentiate uptake inhibitors, or carefully potentiating the action of monoamine oxidase inhibitors with tricyclics, though the warnings said not to. I learned about

potentiating both antidepressants and antipsychotics with small amounts of thyroid hormone in euthyroid psychiatric patients, and the use of lithium to reduce impulsive acts, such as suicide or binge drinking or gambling. The addition of tryptophan to a monoamine oxidase inhibitor regime potentiates their antidepressant effects. S-adenosylmethionine can be useful as a health food, over the counter antidepressant. I learned these and so many more things.

Every two years we went to another Caribbean Island. When we went to Haiti, Nate arranged for us to spend a few days with voodoo priests, who had various potions that served as the vehicle for the transformation of a person into the walking dead, a zombie. We took a little and found that it slowed the heart and respiration, as well as temperature and metabolic rate, so someone could be buried alive for several hours and then return. We also learned how the zombie ceased to exist to the society. They walked by him as though he weren't there. Nate took some of the potion to his labs, now the Nathan Kline Institute, for analysis. We never heard more about it. Nathan wouldn't talk. Incidentally, I appointed Nate Kline a part time Clinical Professor in my Department of Psychiatry at UCSD in La Jolla. I was happy that he claimed this affiliation in his books.

DH: As I understand it, when you started the Department of Psychiatry at UCSD in 1968 you had a relatively free hand in recruiting and were given many FTEs. Is that true?

AM: It's hard to believe, but in addition to several clinical billets at UCSD's VA Hospital and more at its County University Hospital, I got 12 tenure track academic positions. And once again, I was faced by the state of psychiatry at that time, a split between a dynamic, interpersonal orientation and a behavioral neurobiological position. How I solved this problem may have more general importance.

My first hire was Sam Barondes, who was a well-trained psychiatrist as well as an accomplished molecular biologist out of the laboratory of Nierenberg, the Nobel Prize winner. For 1969, that was a strange combination as well as a unique appointment in a department of psychiatry. He worked on problems ranging from RNA in memory transfer, membrane-involved glycoproteins in cellular organizations like the transition of the slime mold to a fruiting body when food gets short, and, other fundamental biological problems. He wound up Chairman of the Department of Psychiatry at the University of California in San Francisco.

My second hire, Lew Judd, was a very promising child psychiatrist and clinical researcher. His career path in our department led to his being head of the National Institutes of Mental Health for a time, before taking over my chairmanship at USCD. Almost every kind of psychiatry was

represented in our department. Psychoanalytic clinicians were intimately involved in training our residents, as were the brain chemists and molecular biologists.

In addition, we developed a deep area of neuropsychology with the likes of memory theorist, Larry Squire, who was later President of the Neuroscience Society. The residents were also exposed, and often participated in, basic pharmacological studies going on in the department. Even in psychotropic drug treatment, we emphasized the necessity of psychiatrists to have an intimate knowledge of the patient's inner life, whether they used drugs or not. The department also believed in community service.

We established the first methadone maintenance program in California in a network of over 12 clinics with paraprofessional therapists. I went to the University of Chicago for a month and studied with Jerry Jaffe and Danny Freedman, who had the only methadone maintenance clinic after the first one of Vincent Dole's at Rockefeller University. We also established a very sophisticated abortion program involving extensive counseling before and after the procedure. Recall, San Diego was second to only Orange County in Republican Fundamentalism so you can imagine that it made a lot of noise in the newspapers. Between our research and clinical programs our department was receiving several million dollars a year from extramural sources.

DH: From psychoanalysis and molecular biology to methadone maintenance. For its day, it was kind of a wild department.

AM: Even a little bit of potential ACNP gossip comes up in the recruitment context. A Chief of Psychology position opened at the UCSD VAH, and I coupled that with a tenure track appointment in the University and tried very hard to recruit Oakley Ray, with the hidden agenda of moving him and the ACNP headquarters to La Jolla from Vanderbilt. I couldn't get his appointment past the politics of our Department of Psychology, which was anti-clinical and mathematically-experimentally oriented. Several late night committee meetings were to no avail.

That was a loss for us, not just politically, of course. Oakley believed in personality and character as the underpinnings of an understanding of psychiatric disorders and psychotropic drug treatment. He annually used my study of "personality and position in the NFL," published in my book *Nightmare Season*, printed by Random House on 1976, in his classes at Vanderbilt as a way of introducing personality theories.

DH: Before you leave this topic, let me ask you more about the lady, who was actually depressed, who was bonded to Tofranil. Would you describe her change of personality, which is a little bit like the kinds of things Peter

Kramer was describing in *Listening to Prozac*, a very different understanding of what's going on, compared with what has since become the dominant understanding?

AM: Yes, and having tried to equate long term macromolecular changes in response to psychotropic drugs as the underpinnings of drug induced personality changes, it then was a challenge to see if we could develop a research strategy that would reflect objective measures of the change in “style” of the stable state besides the less meaningful change in the mean values of measures. As luck would have it, in the 1960s and early 1970s, applied mathematics and statistical physics was going through a significant revolution with respect to their approach to determinism and randomness in physical systems. I saw that this would give us a way of objectively studying changes in stable neurobiological states.

It was a system of thought and measures across basic clinical neurobiologically relevant variables. I first made contact with this way of thinking in the work of Steve Smale and Mo Hirsch at Berkeley, and Feigenbaum in Los Alamos and, of course, in the work of my good friend Benoit Mandelbrot, then at IBM. I also became close friends with Mike Shlesinger, a world-class statistical physicist. They, generously, spoke with me, tutored me, gave me papers and boy did I study! I studied hours and hours every day and long into the night.

Dynamical systems involved nonlinear differential equations, differential topology, matrix and group theory, nonequilibrium thermodynamics and statistical physics. All this stuff underlies what is now called “chaos and fractals”. How to characterize the behavior of whole systems composed of many coupled parts, such as brain and behavior and its psychopharmacology, were natural contexts for the study of complex systems.

I organized the first conference about this relevant to psychiatry “in the world”, at the annual meeting of the ACNP in 1982! It involved Mark Geyer, Cindy Ehlers, Suzanne Knapp, Pat Russo, and others. I tried to explain this area of research to the psychopharmacology community in the *Annual Review of Pharmacology and Toxicology* in 1984. Then I got the NIMH to sponsor an international conference with the mathematical, physical and biological leaders in the field held at the auditorium in the intramural program at NIMH. There were about three hundred attendees. They ranged from mathematicians to clinical psychiatrists with many physicists. It was published as Volume 504 of the *Annals of the New York Academy of Science* in 1987.

It was about this time that it was clear I was committing the rest of my life to chasing this fusion of nonlinear dynamics and statistical mechanics as applied to neurobiology. It was at this time that I had the great good

fortune to be joined by Karen Selz who was both brilliant and computationally gifted. She saw the blend of qualitative dynamics and quantifiable statistics immediately and we've been working together since. Early in this era of applied dynamical systems, Karen did foundational work elucidating universal classes of dynamical systems styles which mapped onto patterns in human computer mouse behaviour, both of which she related to personality. Then as an encore, she exploited the Thurston-Milnor theorems, showing one could generate any sequence by changing the parameter of the one dimensional tent map, to show that dynamical signs of contrasting personalities could be represented by a single value of a single parameter.

Then, a burst of papers followed, that hasn't stopped. We wrote a personality pattern long paper in *Psychiatry* in 1995. For the most part, however, we have published in physics and biophysical journals as our efforts at intrusion into mainstream psychiatry and psychopharmacology weren't getting anywhere.

The nonlinear dynamics, dynamical systems point of view turns out to be a very powerful way to look at psychiatry and psychopharmacology. For example, in complex systems, there are a relatively few "scenarios", or syndromes. It is paradoxical that the higher the apparent dimensionality of a system, the more coupled the variables, the more likely the system would be to obey only one of a fewer, and fewer set of evolutionary narratives. The implications for brain drugs are many. For example, we all admit now, in spite of the "receptor binding pseudo-specificity" that all effective drugs are "dirty", i.e. critically influence the involvement of many, many mechanisms that we know about, and probably many more that we don't.

In spite of the multiplicity of deterministic mechanisms, we observe a singular, or few, global states of mood and/or cognitive patterns. These patterns can be represented as graph-diagrams in what is called "phase space", with statistical patterns of behavior observed on this phase space. This radical "theoretical reductionism", and not physical reductionism of the "behavior to a molecule" sort, of many simultaneously active systems to behavior that can be represented in two or three dimensions and with one or two parameters, speaks to the essence of dynamical systems. Doesn't that sound like many or most of our researchable problems?

From a measures point of view, it is the pattern variability around the mean function that characterizes the few dynamical states that we can use to study basic and clinical variables relevant to a drug action. These studies turn out to be a deeper look into what had previously been called "noise" or "error". The tools of the measure part of dynamical systems

made it possible to describe “what kind of randomness” we are talking about. One might re-perceive personality as the expected pattern of variation around mean tasks. Not if, but how do you make your bed? Not if, but how do you drive your car? What sort of relationships do you have with others? And the representation can be quite abstract.

Selz has used these techniques on computer mouse trails made by unaware subjects as they carried out simple computer tasks. She was able to clearly discriminate between normal persons with obsessional character, hysterical or borderline personalities. Sometime, the patterns in observables can be diagnostic.. For example, in many systems, increasing regularity augured pathological fixation and stereotypy with loss of flexibility, thus physiological control with resulting disease of the system. Instead of the little ups and downs of normal mood over time, the system becomes coherent at many scales in the form of manic-depressive illness.

DH: How did this kind of thinking show up in your laboratory?

AM: Beginning in the early 1980s I was involved in the application of dynamical systems and measure theory to brain enzyme activity as influenced by psychotropic drugs. Pat Russo and Suzanne Knapp developed *in vitro* preparations that allowed the study of critical brain proteins “in motion”. The fluctuations in the rate limiting enzymes - “product concentration frequencies”-for serotonin and dopamine, tyrosine and tryptophan hydroxylases were studied as time series, and manifested classical chaos and fractal hierarchies of scale in brain enzyme activity. The patterns of fluctuations were sensitive to psychotropic drugs. Lithium decreased the amplitude and increased the frequency of fluctuations in many systems, from tryptophan enzyme fluctuations to spontaneous neuronal firing patterns to the EEG and MEG. Also, it should be noted that it was in our laboratory that Mark Geyer began his remarkable program of work leading to startle habituation and its failure as an animal marker for antipsychotic and other psychotropic drugs. Martin Paulus translated the ergodic theory of dynamical systems into the analysis of varying partitions of time series of rat and human behavior in such a way that an entirely new set of measures were used to demonstrate drug effects, strain differences, and with David Braff, psychopathology in man. This occurred in the 1980s and early ‘90s.

DH: It all sounds very exciting but honestly, I haven’t seen much evidence of this point of view on the current psychopharmacological scene, either in clinical or basic research.

AM: That’s a personally painful truth. I, and my co-workers, have spent years working in dynamical systems in brain and behavior, and little by little it got corralled into biophysics. Physics, biophysics and dynamical

systems meetings are those that this kind of work gets presented in. I received a MacArthur Prize Fellowship in theoretical neuroscience from 1984 to 1989, the money from which I used to spend years at European mathematics institutes known for these kinds of mathematics and physics.

Rene Thom invited me to the Institute des Hautes E'tudes in Bur sur Y'vette twice, for a year each time. Both times were buried in studies with their very generous and helpful mathematicians, particularly David Ruelle. From Thom, I learned differential topology; and from Ruelle, ergodic theory and statistical mechanics. I then spent almost a year at the Warwick Mathematics Institute as a guest of Christopher Zeeman who taught me bifurcation theory and then I studied with their world-class ergodic theorists: Peter Walters, David Rand, Tony Manning and Mark Pollicott.

Karen Selz, who has a joint degree in mathematics and psychology and I wrote dozens of papers using these theoretical and computational methods in cardiac dynamics, brain stem neuron time series, EEG, and human behavior, all with implications for psychopharmacology. With Knapp and Russo, I showed these kinds of dynamics in substrate to product concentration fluctuations of biogenic amine enzymes and their receptors. The first report on this was out in the first volume of the Journal of Neuroscience in 1981. Sharing one of Roger Guillemin's grants at Salk, I began to apply symbolic dynamics to analyse and predict amino acid sequences as hydrophobic moieties to see if that might "match" ligand and receptors. The scheme was not much good. It was then, that my co-worker, Selz was inspired to use a particular system of eigenfunctions, hydrophobic eigenfunctions, which demonstrated matches between ligands and their receptors. Selz and I used these techniques to successfully design dopaminergic and muscarinic peptides that modulated the sensitivity and allosteric properties of the D2 and M1 receptors. Leon Glass, the Canadian physicist, took this point of view into cardiology and brain science. Paul Rapp, an Oxford mathematician and Drexel University physiologist was a major contributor to applying it in EEG, psychotherapeutic interactions and other aspects of brain science. Jim Collins and his group at Boston University, and Ari Goldberger, once a post doctoral student of mine, with a very large nonlinear dynamics center at Harvard, are major contributors to physiological research using dynamical systems methods. Cindy Ehlers at Scripps Research Institute has applied these techniques to the analysis of neurophysiological data. But except for an occasional inspired physicist writing in physics or biophysics journals, very little has found its way into the literature of psychopharmacology or psychiatry.

DH: What has any of this new field amounted to as far as the research or practice of top-drawer psychopharmacology as represented by the ACNP membership?

AM: Actually, very little. Following the dynamical systems panel I arranged at the ACNP annual meeting in 1981, I have been unable to present or publish about this field at psychopharmacology meetings or in its journals. For example, since the 1980's the ACNP program committee has rejected high quality panel submissions, composed of the best and most accessible mathematicians and physicists. I suspect if I didn't have the energy and smarts that Karen brought to our work, I was ready to quit.

DH: Why is that?

AM: Besides the deep suspicion and dislike of most biologists about things mathematical, I would say it was the excitement of the more concrete and obviously biologically relevant competing fields. The incredible technological sophistication and ease of modern molecular biological techniques, the emergence of microfluidics and high throughput screening methods, as well as the intuitive appeal of modern brain imaging that take psychiatry back to our turn of the 19th Century neurologizing, has all but masked this emergence of dynamical systems theory and its attendant methods.

DH: Can you give some examples of how dynamical systems thinking might be applicable to a practicing psychopharmacologist?

AM: I have three favorite examples, though I could give you many. Most psychopharmacologists are probably familiar with both phenomena, but don't think of them from this perspective. The first involves nonlinear dose-response curves. By that, I don't mean "S" shaped curvilinear functions, but a result of a nonlinear function, or operator $f(x)$, defined by what it is not. In a linear operator 2 times $f(x) = f(2x)$. In a nonlinear system, 2 times $f(x)$ doesn't = $f(2x)$. In such systems, in some drug dose regimes, more drug leads to less effect and/or less drug leads to more effect.

Back in the tricyclic days, before the popularity of the SSRIs, much work was done with tricyclic blood levels in relationship to clinical efficacy looking for "the therapeutic window". This is quite a general property of psychotropic drugs, which may even demonstrate iterative saturation plateaus. This implies that one might be able to treat a psychiatric disorder optimally with very low doses of drug, then again at medium doses of drug, and then again at high doses of drug. This also means that if one is not getting the desired effect, there are dynamical arguments for lowering the dose as well as for increasing it. Of course, with respect to side effects, finding the lowest effective dose would be desirable. I would

also say in this context that PDR recommended doses for psychiatric drugs have less meaning than in more simple systems.

The second example is what might be called the “curse of polypharmacy”. Since the dynamics of complex nonlinear dynamical systems representationally simplify with more and more parameters, a patient with a complex psychiatric illness whose personal pharmacopoeia reads like a drug store pharmacy is not necessarily being poorly treated. A carefully followed patient with whom a physician is using drug choice and dosage range on a trial and error basis may eventuate in a treatment program that includes, for a real example, three antihypertensives, two or three antidepressants, a β -blocker, a calcium channel blocker, a bone saving biphosphonate, a personality changing antiepileptic, a stomach saving H_2 transport blocker, aspirin, a prostaglandin blocker, lactoferrin, ascription, a calcium-magnesium supplement and some herbal preparations.

Two generally true circumstances underlie the theory of thoughtful, therapeutic polypharmacy: (1) Drugs given for a single somatic locale act on biochemical mechanisms throughout the body in such a way that their nonlinear interactions can produce an unknown except empirically global physiological state of health; (2) The more independent variables, “handles” to manipulate, the greater the likelihood of finding and stabilizing even a small available parametric space of healthy function while minimizing unwanted effects. Rene Thom, Chris Zeeman and their students studying discontinuities, “bifurcations,” “catastrophes” real dynamical system, such as the regulation of thyroid function and immunology, proved that the more dimensions, “controls,” “handles”, one adds to a nonlinear system, the easier it is to find and stabilize a very small island of health totally surrounded by oceans of disease.

Another example is the remarkable observation we made on the saturation kinetics of brain tyrosine hydroxylase, the rate-limiting enzyme for dopamine and norepinephrine. We saw iterative saturation plateaus with bifurcations, discontinuities between sequential regimes. We saw different sizes of dose response curves suggesting that for some brain systems there are very low dose efficacy and very high dose efficacy regions. This confirms some clinical experience. I truly believe that for given patients and under propitious circumstances, one can obtain remarkably good clinical results with very low doses, far below the recommended dose. What one is looking for is the therapeutic island, not a sufficient amount. Dynamical systems give the practitioner a context for many counter-intuitive but phenomenologically observable clinical events.

DH: Why did we lose this kind of view of things during the 1960's and 1970's? Did we lose it because we have gone down into a very phenylketonuric

view of the psychiatric disorders and that's the way they've been leveled here. It's a very antibacterial view, almost. What you're actually describing is something much more subtle and nuance, which has risen its' head under various rubrics every so often over the years, but we've lost it, haven't we?

AM: And the painful part is that the ACNP membership has, in my lifetime, moved from being a revolutionary place of respite and generation of new thinking about brain biology applied to psychiatric disorders, to what I see as a source of conservative inertia. The group feels comfortable mimicking the current basic science found legitimate by internal medicine and other physician groups, but refuses to see itself as a potential font of another whole vision of the human body given by dynamical systems. We who study "dynamics", we who are interested in the "whole person", have resisted the mathematical-physical system of nonlinear global dynamical systems. One of the important mathematicians in this area, Ralph Abraham at UC Santa Cruz, says it will take a hundred years for what I think of as the real underlying scientific basis of psychiatry and psychopharmacology to be acknowledged as such.

DH: How do you feel about that?

AM: I have to resign myself to this opinion, as well as to the fact that I probably won't live to see it. I'm counting on Karen, among a loving few, to carry on and expand the message.

DH: I can see where you're heading been but even me, an English-educated fellow, has had no training at all in this way of thinking. It will need to be reinvented. We've now got managed care. You've got to treat in 15 minutes. How can we ever reconcile that?

AM: I don't know. Right now, I think the very best treatment would be if a general practitioner would give the drugs and manages the side effects, and a psychologist would listen to the patient who gives an account of the changes, if any, good and bad.

DH: The full range of change, right?

AM: Right. Thank you for putting up with me.

DH: It's been absolutely fascinating to listen to another viewpoint. We'll have to reinvent it at some point.

AM: Thank you.

ALEKSANDER A. MATHÉ

Interviewed by Leo E. Hollister
Waikoloa, Hawaii, December 12, 1997

- LH: Today is Friday, December 12, 1997, and we're in Hawaii for the 36th Annual Meeting of the American College of Neuropsychopharmacology. As part of the historical project of the College, we're doing a series of video taped interviews with people who have been in the field for a long while and who, either have made the history of the field or have been witnesses to the great history. Today, I welcome, Dr. Aleksander Mathé* from Stockholm. Your name has always puzzled me. It sounds like it should be a French name.
- AM: Actually, it is. Way back, my family originally came from France. They lived in a part of the Austro-Hungarian monarchy that after World War I became Yugoslavia. So, I was born in Croatia.
- LH: It is quite interesting what happened after World War I.
- AM: Yes. Eventually, I left Yugoslavia, and after all kinds of difficulties I arrived to the United States.
- LH: When was that?
- AM: I guess it was in 1960. Then, I did my rotating internship and then residency in psychiatry.
- LH: You had graduated from medical school in Sweden?
- AM: No, in Yugoslavia. And, then, I came directly to the States and did .one year of internship followed by a residency at Bellevue Hospital, NYU. And, then, I moved to Massachusetts General Hospital (MGH), Harvard Medical School.
- LH: You came just at the right time.
- AM: At the time psychiatry in Boston was heavily psychoanalytically oriented and because of my interest in internal medicine and physiology I was a little bit of an outsider. Luckily, at that point in time, I met Frank Ervin who was also at MGH. He was a staff psychiatrist and a neurophysiologist. He was doing research with reward and punishment mechanisms and that set me on my future path in research, so to speak.
- LH: The idea of the reward systems in the brain was still pretty new then. When was that discovered? Was it in 1957 or 58?
- AM: Sounds correct, but the idea of inserting electrodes and stimulating certain areas of the brain, as you might recall, comes from or at least was developed by Hess, in Switzerland. I think he got a Nobel Prize after showing that cats can be made aggressive or tame by stimulating certain

* Aleksander A. Mathé was born in Zagreb, Yugoslavia (Croatia) in 1934.

areas in their brains. It was the demonstration that one could associate behavior with biological events in brain that had an impact on me.

LH: Was your early work in this area of research?

AM: No, but that was the kind of research that stimulated me to pursue a research career. In 1963, I left the United States and went to Sweden because I got a residency in Internal Medicine at the Karolinska Institute. So I trained in Internal Medicine, first, because I was really fed up with psychiatry at that point in time.

LH: Psychiatry wasn't much of a science you figured?

AM: No, it was not at that time.

LH: Well, I came from Internal Medicine into psychiatry, so we did reverse patterns.

AM: In 1966 I got married in Stockholm, and, then, we returned to Boston. I took a two-year Fellowship at the University Hospital of Boston University School of Medicine in Psychosomatic Medicine. I felt that I might be able somehow to breach the fields of Medicine and Psychiatry. It was an interesting fellowship. There was a strong emphasis on the role personality plays in the development of diseases like hypertension, colitis, asthma, etc.

LH: When you talk about the effect of personality on disease do you mean psychodynamic factors like Franz Alexander is talking about?

AM: Yes, at least in part. My supervisor was Peter Knapp, a psychoanalyst and a professor of psychiatry at BUSM, who was very much interested in psychosomatic medicine and especially in bronchial asthma. So we started to work in this area of research by measuring changes in pulmonary function. We were interested in adrenergic reactions. It was in the same area of research Marvin Stein and Tomas Luparello in New York were involved with. I stayed in Boston for a few years, but, then, I got interested in biochemistry, because I felt that, it's nice to look at physiology, but if one really wants to get deeper into the field of adrenergic reactions, one would need to measure also some other parameters. At this point in time, I started to measure cortisol in plasma and adrenaline and noradrenaline in urine. We discovered that patients with severe asthma had decreased urinary adrenaline and proposed that asthma attacks could be the result of some kind of decreased ability to mobilize adrenaline. Interestingly, some other groups have partly confirmed that people with asthma have deficiency in mobilizing adrenaline.

LH: So, your concept of asthma, then, was adrenaline deficiency?

AM: Yes that could be in part the case.

LH: And, then, later on, the β -receptors are also becoming involved.

AM: Right, and, there was a pharmacologist, Szentivanyi, originally from Hungary, who was to become professor of pharmacology in Florida at the University of Miami, who combined the deficiency in mobilizing adrenaline with the β -receptor changes.

I received an NHLBI Fellowship that made it possible for me to go back to Sweden and work for two-years, from 1969 to 1971, on that topic in the Department of Physiology at the Karolinska Institute. That was the time when Ulf von Euler was at the top of his career. I was in his lab in 1970 when he got the Nobel Prize together with Axelrod, and Katz for their work on catecholamines and acetylcholine, if I remember correctly.

LH: I understand that Ulf von Euler was one of the most self-effacing men in the world. He was very shy and didn't promote himself at all.

AM: Yes, I think you can say that.

LH: Now, again what years were you there?

AM: From 1969 to '71.

LH: Let's see, von Euler got the Nobel Prize in 1970, didn't he?

AM: Right. And it was at the time that the field of prostaglandins started to develop; von Euler was actually one of the people who discovered prostaglandins in 1934, I think, although he did not get a Nobel Prize for it. Subsequently, other people, Vane in the UK and Bergström and Samuelsson at the Karolinska got the Nobel Prize for the prostaglandins; although, it was Von Euler who in the mid-1930s started the research that lead to the prostaglandins.

LH: He gave them their name.

AM: Right. During the two-years I was at the Karolinska I was involved in research with monoamines, prostaglandins and psychosomatic medicine, primarily geared towards asthma and allergic reactions. Then, after two-years, I started to work for my PhD thesis in the same department and also collaborated with people in the department of pharmacology.

LH: What was your thesis on?

AM: It was focused on asthma and dealt with prostaglandins, monoamines, cyclic AMP and cyclic GMP. Until that point in time asthma was attributed to histamine hyper-reactivity, and I discovered that in the pathogenesis of asthma prostaglandins play also a role.

LH: I guess that was kind of a beginning of a shift in emphasis in asthma from immunological changes to inflammatory changes.

AM: Yes, perhaps. We returned to the States, I became a faculty member at BUSM in the department of psychiatry, got a NHLBI grant, and continued my research. The Head of the Institute used to joke that I was the only psychiatrist they trusted enough to support. Although I did some

research in measuring plasma cortisol levels after stress, my research focus remained on prostaglandins and also on leukotrienes. At that time, the name of leukotriene was not yet coined. It was called SRS, slow reacting substance. So, I continued doing that research for a number of years while keeping one foot in the lab and one in psychiatry.

LH: For someone trained in psychiatry, as well as internal medicine, what better place?

AM: Yes, so, that was really nice. And, then, time went by and it was Sy Fisher who invited me to the annual ACNP meeting.

LH: Was that your first meeting?

AM: That was my first meeting and it must have been like 1974 or '75. The reason I remember it, because it was in Palm Springs and I don't think many meetings have been held there.

LH: I think that's the only time we've ever been in Palm Springs.

AM: But, it must have been in the early '70', right?

LH: I'm sure it was. I can't give you the date, but it was around that time. So, what did you think of the organization?

AM: I thought it was a serious organization and realized that future belongs to neuropsychopharmacology. It was also a field geared towards monoamines, which certainly interested me. So, I, then, decided that I'm going to get again more involved in psychiatry. I was attending a few patients and had some teaching responsibilities, but was doing mostly laboratory work. About that time together with people from the departments of pulmonology and biochemistry at the University Hospital of BUSM we got a large center grant from the NHLBI, and, Peter Knapp and I were collaborating with the people from the other departments in studying the medical and psychological aspects of allergy and lung diseases. Then, in 1976 I defended my PhD thesis at the Karolinska Institute, and, in 1977, I went back on my sabbatical from BU to the Karolinska Institute. It was during that year that I started measuring prostaglandins in CSF and found some changes in certain prostaglandins in the CSF of schizophrenics. This whole issue about prostaglandins and schizophrenia so, has still not been resolved.

LH: Did you ever measure prostaglandins in Alzheimer's patients?

AM: No.

LH: There's a feeling now that some of these prostaglandin and synthetase inhibitors might be useful for slowing down the course of Alzheimer's disease.

AM: I came back from Sweden in '78. There was still very little research going on at BU. It was still very heavily psychoanalytical. Then, I met Ken

Davis at one of the conferences. It must have been the Catecholamine Conference in 1978 in Asilomar, California

LH: Was it that long ago? It's almost 20 years.

AM: Yes. Ken was, at that point in time, recruiting his crew to move to Mt. Sinai in New York. I think it was in the summer of '79.

LH: He really shook up that department.

AM: Yes. Then, I joined him and that's how I really got a hundred percent into psychiatry and psychiatric research. It was then for the second time that I went to attend the annual ACNP meeting. I think it was the meeting in '79. And I haven't missed one single meeting since.

LH: Well, you are a foreign corresponding fellow.

AM: No, I'm not.

LH: How did you get here?

AM: Well, I get always an invitation from someone.

LH: Well, you should have some membership status.

AM: Yes that would be great.

LH: Well, they ought to find some niche for you in the membership category. We're having less and less participation in these programs by ACNP members. And, here you are, participating actively. You should be an ACNP member.

Well, what do you think in terms of looking back on the old psychodynamically based ideas about causing duodenal ulcer, asthma, irritable colon, or other disorders? Many of the disorders that were thought to be psychosomatic, over the course of the years, have been shifted into another category. Duodenal ulcer is an outstanding example. Now, it doesn't seem to matter a damn bit whether you were breastfed or not or all that stuff we used to talk about, because it's a matter of whether you've got the helical bacteria. What would you do if you were in psychosomatic medicine today? What line of research would you follow?

AM: Actually, I think that it would be difficult to dissociate any disease from psychological factors. In fact, there's a book on asthma, that is revised every four years and it has a chapter on the psychological factors in asthma. But, what I think important is the fact that once you have a disease it may flare up or be attenuated by psychological factors.

LH: Oh yes. By the same token, you know, I like to think that, for some disorders that might be called somatopsychic a reversed situation might be the case. For instance, one of the concepts with asthma, early on, was an overprotective mother, and I guess some people, at a hospital in Denver, used to talk about treating it by parentectomy, i.e., removing the child from the parent to help them. But, when you think back on it, asthma,

to a parent, must be a terribly frightening thing, just as it is to the child, and, of course, parents become overprotective. But, that may not be necessarily causally related to asthma at all. It may just be a reaction to the illness, itself. It might be just like a reaction to a psychological event. Does that make sense?

AM: Yes, a lot of sense. So, when Ken recruited me I started to do other research. It was mostly with cortisol, ACTH, prolactin and growth hormone. It was a new kind of endocrinology in depressed people and schizophrenic patients. I was a member of his team. So, I stayed with him at Mt. Sinai for four years until 1983. And, then, I got an offer from the Karolinska Institute to return to the Department of Psychiatry. Since my wife is Swedish, we had a tough decision to make because professionally it would have been better for me to stay in the United States. But, for personal reasons, we decided to go back to Stockholm and work at St. Goran's hospital.

LH: Now, is St. Goran a psychiatric or a general hospital?

AM: It's a general hospital.

LH: With a psychiatric wing?

AM: Yes. It is affiliated with the Karolinska Institute; it's one of its teaching hospitals. I started at St. Goran's Hospital in 1983 and I've been there ever since. So, it's now fourteen years. I got involved in general psychiatry, seeing patients mostly with affective disorder. Then, in '85 or '86, I became responsible for organizing the psychiatry course for the medical students at the Karolinska Institute. I do some teaching myself, but my primary responsibility is to see that the students are properly taught, that the content of what's being taught is appropriate, etc.

LH: Well, it's nice to see a researcher, who is interested in teaching.

AM: I continued of course my research all along. Neuropeptides have been a hot issue at the Karolinska; a number of them were discovered there, and some of the methods to measure neuropeptides were developed there. So, gradually we started to look at the effect of lithium on neuropeptides and the effect of ECT on neuropeptides and that has been my two lines of research since then. There are several hundreds of neuropeptides and I measured about 12 or 15, but we found that only two of them, neuropeptide Y and neurokinin A are affected by ECT. These findings have been, by now, replicated by a number of other laboratories.

LH: It must be real.

AM: It's a selective effect and it does not occur after one treatment. One has to give a series of ECTs to get it but the effect persists for two to four weeks after the last treatment. We do microdialysis in vivo, so that we can actually look at the release of neuropeptides and not just measure them.

I also did a study in collaboration with NIMH. They treated some patients with ECT and sent me their CSF from before and after ECT. The findings in my first study and the collaborative study with NIMH were the same. The results of these studies were published, I think, in '94 or '95.

LH: Did you find any changes in ACTH?

AM: We measured NPY, endothelin, and neurokinin A but not ACTH. So that's a line of research that I have been doing lately; much more in rats than in patients. I also started looking at the effect of lithium on neuropeptides. I think, Mimo Costa was the first in 1978 to publish a paper on the effect of lithium on neuropeptides. I think he measured endorphin, or maybe it was enkephaline, but he didn't continue with his research. I picked it up and continued.

LH: What did Mimo do?

AM: He administered lithium orally for six or seven weeks to the animals; then, took their brains out and looked at changes in peptides. We confirmed his findings but in our study we also measured messenger RNA.

LH: Well, what do you make of the CRF story, so far?

AM: It seems to be an important peptide but I've not been so much into CRF. Since there are so many peptides you have to limit yourself and choose some that you find of potential interest. In addition to endogenous peptides we also looked at the effect of lithium on cFos, and AP1 binding in collaboration with Jeanette Miller at NYU and found that lithium has an effect on them. And we are currently still working in this area. Our aim is to contribute to the understanding of how lithium works.

LH: This is remarkable. One would think that a simple ion like lithium would not have so many diverse physiological effects. Of course, the discovery of the therapeutic effect of lithium in psychiatry was completely accidental. How about any other ions? I remember back in the days when we used to use bromides. I would think if we had the current measurements to monitor blood levels, bromides might not be too bad as anti-anxiety drugs.

AM: I've never used the bromides, so I can't comment

LH: Oh, they were out by the time you came along. I'm thinking back in the 1940's. At that time people didn't have any guides to how to use them properly. With the current methods of monitoring, one could imagine it would have been possible to keep the levels low enough that one would not get into the trouble of toxicity people got into before. Calcium channel blockers are a hot topic these days; although, I think there's more heat than light about their effectiveness. Let me ask where are you going from here with your research?

AM: I'm doing some research with ECT and trying to find out whether it is the seizure or the low voltage fast activity after seizures that is responsible for its therapeutic activity. I have been studying the effect of benzodiazepines and anti-epileptics on ECT.

LH: Any drug you are studying specifically?

AM: MK-801. It's a classical NMDA channel blocker. It was experimentally used in England in humans but the problem is that while it has antiepileptic, anti-seizure activity it is also a psychomimetic. We started to give it to rats and discovered that MK-801 has an effect on some neuropeptides. Now, we are looking into the effects of other compounds, like PCP, amphetamine, on neuropeptides, in the rat, of course. With regard to antipsychotics, we looked at haloperidol and risperidone and found that they have distinct effects on some neuropeptides in the brain. And they also block the effects of psychomimetics. That's the field of research I intend to pursue very vigorously.

LH: It would be nice to be able to explain why the atypical antipsychotics have the advantages that they are purported to have.

AM: Right. Maybe the difference between typical and atypical antipsychotics is in their effect on other structures than dopamine receptors. Charlie Nemeroff and others have been exploring neurotensin in psychosis and also the effects of antipsychotics on neurotensin. I'm doing research in the same field, but looking at different peptides like NPY and CGRP. There were papers in 1996 in the *Journal of Neuroscience Research* in which it was reported that amphetamine, PCP and some other compounds are potent releasers of CGRP in addition to releasing dopamine. It seems to me that there is a new field in development that deals with interactions between certain peptides and dopamine.

LH: Well, that may be the way to go to explain the purported differences between typical and atypical antipsychotics. I'm not impressed by the differences in their effects on receptors and I don't see any pattern that makes sense. There is just no evidence that D_4 receptors have a damn thing to do with schizophrenia. In fact, we don't know what D_4 receptors do. The only common feature of atypical antipsychotics is that they're weak D_2 receptor antagonists. But, there must be other differences that may very well reside in the peptides, because there's really very little evidence that the other receptors that have been implicated contribute anything to their clinical effects.

AM: Just back to the work on lithium for a moment. All my work on lithium was done initially on healthy male rats. And, then, we decided that we should do also females, and today we are using, both, male and female rats. Moreover, we are systematically looking at the effects of ECT and

antidepressant treatment on neuropeptides in different strains of rats and found different effects in different strains. Currently, we are using strains called Flinders Sensitive Line and Flinders Resistant Line. That's a strain David Overstreet breeds at the University of North Carolina. After he developed this strain of rats in Australia he took some back with him to the United States. So, now, he breeds these two strains of rats. They display different behavior from other rats and have a hypersensitive cholinergic system. It is much more interesting to test ECT and antidepressants in some kind of diseased rats like these ones.

LH: Well, let's see, it's been about 25 years that we've known about neuropeptides. I guess we've learned a helluva lot, but it's hard to put it together in any coherent fashion, I think, in terms of formulating hypotheses, but maybe that's my problem.

AM: No, I don't think it's your problem. I think it's simply due to the fact that there are literally hundreds and hundreds of peptides in nature. Only some, far from all of them, are found in human. In addition, we should remember that all peptides are broken down into fragments, some of them inactive and some of them active. Moreover, some of these fragments have the opposite effects from their parent compound. So, it's not possible to suggest that you take them one by one and see how many of them are in a given brain structure.

LH: It's like trying to play a card game with an incomplete deck.

AM: Or, it's much more like playing chess. You have 32 pieces and a huge number of possible moves and combination of moves.

LH: Well, you've had a very rich career and covered a lot of bases, coming all the way from asthma up to neuropeptides, and I rather expect to hear a lot more about them in the next few years, thanks to you and some other people working in the field. But, what happened to that fellow, who was the first to describe neuropeptide Y?

AM: Tatemoto and Mutt.

LH: Yes, Tatemoto.

AM: I don't know where he is now. Interestingly, the other person, Victor Mutt, is still very active at the Karolinska Institute. He is 76 or 77 years old and just recently discovered a peptide that's very important for diabetes.

LH: Well, I wonder about Tatemoto, because he would still be a very young man, probably in his 50's, I guess.

AM: I have no idea.

LH: Well, anyway, it was nice talking to you about this frontier in psychopharmacology and I think that somehow or other, ACNP is missing a gut in not having you in some membership status.

AM: I intend to keep coming to every single meeting.

LH: Well, you shouldn't be dependent upon the charity of strangers. That's a line from the movie *Streetcar Named Desire*. You should be able to do it on your own membership. It was so very nice talking to you. I learn so much from doing these interviews. I had very little idea of many of the things you were talking about, but I think I can appreciate the value of them.

AM: Thanks.

LH: OK.

CHARLES B. NEMEROFF

**Interviewed by Thomas A. Ban
Acapulco, Mexico, December 13, 1999**

TB: We are at the 38th annual meeting of the American College of Neuropsychopharmacology at the Acapulco Princess in Acapulco Mexico. It is December, 1999, and I will be interviewing Dr. Charles Nemeroff.* I am Thomas Ban. Let's start from the very beginning. Could you tell us where and when you were born? If you could say something about your early interests and education.

CN: First, it is an honor to be interviewed for the ACNP archives. I was born in 1949 and brought up in the Bronx. I attended the New York City public schools and, in fact, like many of us in those years had the opportunity to skip the eighth grade. In 1966, I graduated from George Washington High School in New York, which is the high school Rod Carew, the Hall of Fame baseball player attended. I then attended the City College of New York like many of my heroes including Julie Axelrod and one of my key mentors, Morrie Lipton, who I will talk to you about later. After attending the City College of New York, I moved to Boston, where I started working at McLean Hospital in their research laboratories. This facility was obviously much smaller than it is today and I worked as a research assistant in the laboratory of Victor Shashoua who at the time was studying neurochemical changes in the brains of goldfish after a new learning task was accomplished.

TB: How did you get that job?

CN: I obtained that job because I had worked in the Department of Ichthyology at the American Museum of Natural History in New York. I was supported by a small NSF grant during my undergraduate years in New York; this was my first exposure to research. With this experience in ichthyology I got the job, because there weren't very many people that knew how to handle goldfish, I was hired in 1970 as a research assistant at McLean Hospital, a major teaching hospital for the Department of Psychiatry at Harvard Medical School. Once there, I started attending various research seminars. This was a very exciting time, and there were many, many, seminars.

TB: Could you tell us about the people who worked there at the time?

CN: The laboratory was directed by a very dynamic neurochemist, Jordi Folchi-Pi, who had come from Spain to the United States. There were a number of other investigators there, Harvey Shein, a psychiatrist, George

* Charles B. Nemeroff was born in the Bronx, New York in 1949.

Hauser and Joseph Eichman, neurochemists and others. It was a very exciting time and I had the remarkable pleasure of meeting Alfred Pope, the head of neuropathology at McLean Hospital and a professor of pathology at Harvard. He had worked with Oliver Lowry in pioneering microchemical studies of the cerebral cortex. He, in fact, was the person who with Oliver Lowry had invented a quartz microbalance scale so that he could actually weigh each layer of the cortex. And, what Alfred did, in those years, was to dissect each of the layers of the cortex and, then, measure, with very elegant techniques various enzyme activities. This was really the beginning of modern quantitative neurochemistry. Alfred had no children; his wife was a psychiatrist at Massachusetts General Hospital. He took me under his wing and mentored me, almost as a surrogate child. I enrolled into the Master's degree program at Northeastern University, in Boston. It was interesting. I applied to several graduate schools in the Boston area; the chairman of biology at Brandeis University, in Waltham, Massachusetts, said I would never amount to anything and that I should keep my research technicians job at McLean and not attempt to apply for any higher degree. I remember leaving his office rather crestfallen but Alfred Pope continued to be enthusiastic about my graduate school and medical school training. Alfred Pope served as an adviser for my master's thesis and virtually every day after work we would sit down and use the double-headed microscope in his office and go over the studies that I have been conducting on the blood-brain barrier for my master's thesis at Northeastern. These were studies that demonstrated that during seizures the blood-brain barrier was reversibly opened, allowing proteins and other substances into the brain that normally wouldn't enter the brain. After I finished my master's degree, Alfred said to me, "you must get a PhD, and I think you should get a PhD in neuroscience".

TB: Where did you get your PhD?

CN: There were only three universities in the United States in 1973 that offered neuroscience PhD degrees that I was aware of, the University of Florida in Gainesville, the University of Illinois in Champaign Urbana, and the University of North Carolina at Chapel Hill. Having been brought up in New York City I certainly did not want to live in cold weather. I ultimately ended up deciding to go to Chapel Hill, where I almost immediately met two individuals that would irrevocably change my life: Morrie Lipton and Arthur Prange. Both of these individuals are past presidents of ACNP. The reason I ended up going to Chapel Hill, and not to a program I was accepted into at Duke, in Durham, North Carolina, was primarily because Duke had a double language requirement for the PhD degree and I knew that I would have had difficulty with that requirement.

TB: Could you tell us something about Morrie Lipton?

CN: Morrie was one of the most remarkable individuals I have ever met. He earned his PhD degree in biochemistry from the University of Wisconsin and an MD degree from the University of Chicago. Both he and Art Prange were psychiatrists. One of Morrie's remarkable attributes was that he was as comfortable talking to the fellow that mopped the floor in the research building where we worked as he was talking to the Dean or the President of the University. He was truly egalitarian and that is something that has stuck with me and something that I have tried to emulate. At any rate, I ended up working with Art Prange for my PhD degree.

TB: So you ended up working with Art.

CN: He was my doctoral mentor. My PhD dissertation was on the Effects of Thyrotropin Releasing Hormone (TRH). In those days, neuropeptides were just being discovered in the brain and no one believed that they had effects on the brain, other than endocrine effects mediated by their actions on the pituitary. I remember, time after time, our abstracts documenting CNS effects of peptides submitted to the Endocrine Society for presentation at their annual meeting were routinely turned down for presentation because their leadership did not believe that these peptides were really neurotransmitters. Art Prange was a fabulous role model, because he conducted both basic science research and conducted clinical research, a true translational scientist, and was a fabulous mentor. Part of being a good mentor is to know when students should be left alone and other times when they need direction; Art was very good at that, and he let me stumble around a bit as I progressed with my PhD studies.

TB: When did you get your PhD?

CN: I completed my PhD in 1976 at the University of North Carolina at Chapel Hill, applied for and awarded a Fellowship stipend from the National Institute of Neurological Disorders and started to work in the laboratory of an internist-neuroscientist in order to begin to learn, molecular neurobiology was then an emerging area. My postdoctoral mentor was Steve Kizer who had trained at NIMH with Julie Axelrod and Mike Brownstein. I spent a year working with Steve and I learned several things. First, it taught me that I didn't do well in a laboratory that had no windows and it taught me that I missed interacting with a large number of students and fellows.

With Morrie Lipton and Art Prange's encouragement, I ended up applying for admission to the UNC medical school and I began as a medical student in 1977. I graduated from medical school in 1981 and, then, began my internship and residency at UNC where I met Dwight Evans, who is a member of the ACNP. Dwight, at the time, was a junior attending

on the inpatient psychiatric service at UNC. Over the next four years we probably published ten to fifteen papers together, largely studies of pituitary-adrenal and pituitary-thyroid axis abnormalities in patients with mood disorders.

TB: Didn't you work at Duke at a certain point in time?

CN: I was recruited to Duke University Medical Center with my colleague, Garth Bissette. This was an exciting time in neuroscience and psychiatry. Ranga Krishnan, Saul Schanberg, Ted Slokin and Redford Williams were there, as was Clinton Kilts. I had a variety of graduate students in pharmacology who conducted their PhD research in my laboratory including Mike Owens, who is a member of the ACNP, and Beth Levant, a faculty member at the University of Kansas, and a variety of other fellows and students. We stayed at Duke from 1983 to 1991, and during those years our laboratory focused largely on neurotensin, a thirteen amino acid-containing peptide that appears to be involved in the mechanism of action of antipsychotic drugs. We also began study of corticotropin-releasing factor (CRF), which was discovered in 1981. This forty-one amino acid-containing peptide that controls the pituitary-adrenal axis appears to be hypersecreted in depression and perhaps in certain anxiety disorders; CRF receptor antagonists are a novel class of antidepressants and anxiolytics that are currently being developed.

TB: When did you move to Atlanta?

CN: In 1991, a remarkable opportunity arose that was simply too exciting to pass up and that was the opportunity to relocate to Atlanta to Emory University where the Chairman of the Department of Psychiatry, Jeffrey Houpt, had become the Dean of the School of Medicine. With the sizeable development package provided to me by the university, we were able to recruit a number of talented new faculty, many in collaboration with other departments. These included Michael Davis from Yale, a leading behavioral neuroscientist, Clinton Kilts from Duke, a PET imager and extraordinary analytic neurochemist and Tom Insel from the NIH, who became Director of the Yerkes Primate Center and, then, eventually the Head of the NSF-funded Center of Behavioral Neuroscience. Jay Weiss, one of the leading investigators in animal models of depression, joined the department as did Michael J. Owens, my former graduate student and fellow, William McDonald, one of the leading investigators of ECT and now transcranial magnetic stimulation and head of medical student education, and Paul Plotsky from the Salk Institute. We have gone on to continue to recruit young MD/PhD's and MD's and in the almost nine years that I have been at Emory the department has grown considerably in terms of its research portfolio. We have been able to receive generous

support from philanthropic sources and substantially increase our NIH funding.

TB: What are you working on now?

CN: In recent years, I have focused largely on the long term neurobiological consequences of early trauma. As I am sure you know, we have an unacceptably high rate of child abuse and neglect, not only in the United States, but worldwide. We have also been conducting studies in laboratory animals, rodents and non human primates, as well as clinical studies, showing very long term consequences of maternal neglect. We believe that the consequences, which are changes in the activity of the HPA axis, changes in CRF gene expression and changes in a variety of other neurotransmitter systems, underlie the vulnerability of these individuals to the development of mood and anxiety disorders. We are now beginning several treatment studies in this clinical population and my hope is that eventually we can begin to look at prophylactic treatment to prevent depression in this “at risk” group.

When I look back at the career that I have had, I have been lucky. I have been fortunate to have a fabulous family. I have had a fabulous team of colleagues, support staff, junior faculty and, perhaps, most importantly in relationship to this current interview is the remarkable friendships that I have made with ACNP members. These individuals, just to name a few, include Jack Gorman, Ned Kalin, David Rubinow, John Newcomer, Jeffrey Lieberman, Peter Kalicas, Dennis Charney, Marty Keller, Danny Weinberge, Dwight Evans, and Alan Schatzberg. They have become best friends to me and my family because we all travel a great deal to a variety of meetings. This is one reason why the American College of Neuropsychopharmacology isn't just a professional society like the American Medical Association or the American Psychiatric Association. In contrast, the ACNP is a college, meaning that the individuals are collegial, and I could probably name twenty or thirty individuals, who I feel sufficiently close to in this college, that I could go to with any personal or professional problem that might arise, either, in my department or in my personal life. And, I believe that's why the ACNP means so much, to so many of us. Of all the organizations I belong to, and I have multiple affiliations with a variety of organizations, this is the organization I feel closest to, and I know that my colleagues would echo these sentiments as well. I was an ACNP travel awardee and became a member, though my membership application was rejected the first time I applied, a not unusual occurrence, as you know. Eventually I became a fellow, a member of the council and was elected president. The ACNP is very important to me. And, not only have my relationships with members blossomed, but with their spouses and children as well. In life it

is not only the good work that we do, which hopefully translate into better care of the patients that we have spent so much time caring for over time, but, also the friendships we have, which, in fact, contributes a great deal to the quality of our lives. It is for that reason that so many individuals have put so much time and effort, without remuneration, into this college. We have lived through fabulous times here at the college and we witnessed tragedies. Morrie Lipton, one of my mentors, suffered a CVA at an ACNP meeting in Puerto Rico several years ago. I think of the ACNP, as a family, usually functional, but occasionally dysfunctional, with occasional squabbles among its members, as one would expect from a talented, intelligent and strong-willed group of family members. There isn't any other organization that combines excellence in neuroscience, clinical psychopharmacology; epidemiology, genetics, molecular neurobiology and brain imaging that this college does. It suits my needs because I can come to these meetings and learn about areas that I simply don't know enough about, and try to take my own research to the next level. I don't know any other organization like this.

TB: Could I ask you a couple of questions about the research you are involved with in developing new drugs?

CN: OK.

TB: Could you elaborate on that area of activities in your research?

CN: By history, the development of new agents to treat major psychiatric illness has been an area that largely has been characterized as serendipitous. There have been many attempts at rational discovery in psychopharmacology, but in the end, most of the drugs that we have were truly serendipitous discoveries, including antipsychotics, monoamine oxidase inhibitors and even the tricyclic antidepressants. Because of the elegant work of many members of the college that showed hyperactivity of the HPA axis in depression, the discovery of CRF in 1981, led to a series of studies to characterize whether CRF is, in fact, hypersecreted in depression. These studies, virtually unanimously, pointed to hypersecretion of CRF in depression and, not only that, but our and others' laboratory animal studies showed that when CRF was injected into the brains of these animals it produced the full constellation of what we see in patients with depression and certain anxiety disorders including decreased libido, decreased appetite, and disrupted sleep. This work led to the development of CRF receptor antagonists as potential novel antidepressants and anxiolytics. Several pharmaceutical companies have, in fact, developed antagonists to the CRF1 receptor that preclinically exhibit antidepressant and anxiolytic effects. The race is on to determine which company will be the first to demonstrate efficacy in clinical trials. If efficacy is

demonstrated for CRF1 receptor antagonists, then this will represent a new class of agent with a totally novel mechanism of action that may exhibit a broad spectrum of therapeutic activity ranging from post-traumatic stress disorder to major depression to a variety of other disorders, such as irritable bowel syndrome. These agents could even be used preoperatively instead of benzodiazepines to reduce anxiety. The other area that I would want to mention, in terms of drug development, is our work on neurotensin, a CNS neuropeptide that in part mediates the effects of antipsychotic drugs. Basically, what we have discovered is that typical antipsychotic drugs increase neurotensin gene expression and release in the striatum and that appears to predict extrapyramidal side effect liability whereas atypical antipsychotics, the latter including olanzapine, risperidone, and quetiapine increase neurotensin gene expression in the nucleus accumbens, but not in the striatum, and this predicts the clinical efficacy of antipsychotics. The question as to whether a neurotensin receptor agonist might represent a novel class of antipsychotic drug is a very hot avenue of investigation at the current time. No such molecules have yet been discovered.

TB: Simultaneously with your research you have built a very successful department of psychiatry. So, you have administrative, teaching and clinical responsibilities.

CN: Yes.

TB: It has to be a difficult task to deal with all the different responsibilities.

CN: I suppose so. We have about 110 faculty members in the Department of Psychiatry at Emory. Of all the departments at Emory, we are the second best funded department in terms of research. Obviously, a considerable administrative load is associated with running a large department. I have been blessed to have vice chairs that I clearly have to depend on and to whom I delegate tremendous responsibility. Steve Levy, the Chief of Psychiatry at Grady Hospital, is the Vice Chair for Academic and Clinical Affairs and Clinton Kilts, is the Vice-Chair for Research. Because I have a fabulous staff as well as these vice chairs, I have been able to continue my research career and teaching as well. I currently have 3 MD/PhD students that I am mentoring, as well as a number of Fellows. I have a fair number of patients that I still follow, approximately eight to ten hours a week, largely with refractory mood disorders. Then, of course, I have the inevitable administrative responsibilities, including search committees, chair's meetings and the like. Recently I have had an increase in my interactions with the Carter Center, which is also part of Emory, and Mrs. Carter, of course, has a special interest in mental health. I would conclude by saying that one has to love these jobs in order to do them

even reasonably well. I would never suggest that I was very good at all of these tasks but I can tell you that I have enjoyed them. You really have to love your faculty if you are willing to take on the often thankless task of the administrative responsibilities which enable the faculty to be successful. I think the job of the chair of the department is to work as quietly behind the scenes as possible in order to maximize the opportunities for the faculty to accomplish their goals; their clinical goals, their research goals and their teaching goals. If you can do that, without them knowing how precarious this house of cards is sometimes, then, I think you have accomplished your job. I have been very lucky in my life to have the support of great mentors and great students and great colleagues and a great family and would simply hope that all of you watching this video could be as lucky as I have been in the fifty years I have been on this earth and, hopefully, a little bit longer.

TB: During the years you have written many papers. Could you tell us something about your publications?

CN: I have published 600 peer reviewed journal articles, including reviews, many co-authored by my colleagues and junior faculty. The journals in which they are published range from the *Journal of Neuroscience* to *Science*, *Nature*, *Biological Psychiatry*, *Neuropsychopharmacology*, *Journal of Clinical Investigation* and the *Proceedings of the National Academy of Sciences*. I have also had the pleasure of editing the *Textbook of Psychopharmacology* with Alan Schatzberg, currently president elect of ACNP and one of my closest friends. This week the book that we authored together on psychopharmacology for non-psychiatrists, largely for primary care physicians, is, about to be published. I have also edited about 12 other books in the areas of neuropeptides, neuroendocrinology, and psychoendocrinology. I think of all of my publications, the *Textbook of Psychopharmacology* is, by far, my favorite, because it has performed a service for the field. This year, I will complete a four-volume *Encyclopedia of Psychology and Neuroscience* that Ed Craighead, a professor of psychology at the University of Colorado, and I are co-editing. This is formerly *Corsini's Encyclopedia* used largely by psychologists, which we have converted to an encyclopedia of psychology and neuroscience. I am also now working on a CD-ROM project on neuroscience in psychopharmacology for psychiatrists and other physicians, which I hope will be used as a teaching tool to educate about receptors, receptor subtypes, transporters, molecular biology, circuits and cognate areas. I also write a column for the journal *CNS Spectrum* every other month on a topic of my choice, which has ranged from personal columns about tragedies in our lives to topics of professional interest. .

TB: During the years you served on many advisory boards.

CN: Yes. I have served on a number of advisory boards in mood disorders and in schizophrenia. I have worked very hard to try to bring together the pharmaceutical companies and academic investigators to discuss investigations of novel clinical agents, and ethical concerns, such as placebo use in severe psychiatric disorders. I am currently the chair of the Scientific Advisory Board of the National Depressive and Manic Depressive Disorders Association, an advocacy group for patients with bipolar disorder and depression. I am the vice chair of the scientific advisory board of the Anxiety Disorders Association of America, led by Jerilyn Ross, a remarkable individual. Dennis Charney is currently the chair and I have worked closely with him in that organization. I have been involved with the National Alliance of the Mentally Ill (NAMI) and with the Mental Health Association. I serve on a foundation board in Atlanta dedicated to the treatment of patients with mental illness, the George West Mental Health Foundation.

TB: What would you consider your most important contributions?

CN: I think I am probably as good a fisherman as anyone in the college and have tried to convert many ACNP members to fly fishermen. I'd rather be fly-fishing than probably doing anything else except for being with my family. Scientifically, the contributions we have made in the CRF field and the neuropeptide field in general, and, perhaps, some of our work in the serotonin transporter field will stand the test of time.

TB: You have trained many people. Would you like to mention some of them by name?

CN: I have had the chance of working with many superb junior colleagues. Beth Levant was my PhD student, one of the world's experts on the D₃ receptor, and she is on the faculty of the Department of Pharmacology at the University of Kansas. Mike Owens, my first PhD student is on the faculty at Emory, and has gone on to conduct remarkable work on urocortin, the CRF2 receptor and their role in the mechanism of action of benzodiazepines. Jeff Newport, my former Fellow, is now a faculty member at Emory working with Zachary Stowe, another former fellow on depression in pregnancy and in the puerperium. My junior colleagues have been absolutely terrific in contributing to my own work and then moving on to establish their own independent careers.

TB: So you trained quite a number of people who pursue now independently their own area of research, and you have yourself opened up several new areas of research that will hopefully grow.

CN: Well, as you know, Tom, different scientists have different styles. Some work on one distinct area throughout their entire career. Others, like

myself, prefer to conduct research, make new findings and then move on to other areas. Having diverse interests has really kept me going.

TB: On this note we should conclude this interview with Dr.Charles Nemeroff. Thank you for sharing all this information with us.

CN: Thank you, Tom

CARL SALZMAN

Interviewed by Roger E. Meyer
Waikoloa, Hawaii, December 11, 1997

RM: It's December 11, 1997. I'm Dr. Roger Meyer and it's my great privilege to be interviewing Dr. Carl Salzman* in conjunction with the ACNP Task Force, recording the great figures in psychopharmacology. Dr. Salzman is professor of psychiatry at Harvard and the premier clinical psychopharmacologist in the Boston area. He's also been a major figure in developing the field of geriatric psychopharmacology. Carl, what got you started on this trail?

CS: That question goes quite a bit back. I was in medical school and I had no idea whether I wanted to be a psychiatrist. In fact, I was pretty sure I didn't want to be a psychiatrist until I started reading Aldous Huxley and became very involved in reading about mescaline, LSD and peyote. I met Timothy Leary and became very interested in psychiatry through that meeting. Those interests led me to the Massachusetts Mental Health Center, a year after you went there.. And there, I met numerous stimulating faculty, and residents, who were to have a fateful effect on my life. Perhaps the most influentials were Gerry Klerman, and Dick Shader along with Al DiMascio. One of my early supervisors was Eric Kandel; another supervisor was Ed Sacher. In addition to becoming enthusiastic about psychodynamic concepts and psychotherapy, which I still am, I also became enthused about psychopharmacology. I began to do research on benzodiazepines as a resident with Dick and with Al DiMascio. Al took me to a CINP meeting in Washington in 1965 or '66. He introduced me to Jonathan Cole and said, "Jonathan, Carl should work with you". And, Jonathan, of course, immediately offered me a job running the Early Clinical Drug Evaluation Unit. So, I spent my NIMH years working with Jonathan Cole in the Barlow building in Chevy Chase, Maryland from 1967 to '69. By that time, I had already published several papers alone and with Dick Shader. The experience at NIMH and the ECDEU program allowed me to expand my vista in psychopharmacology. I had an opportunity to meet many non-Boston researchers and clinicians -a revelation that there were knowledgeable psychiatrists outside of Boston who had different perspectives than the ones I had learned as a resident - and, at the same time, became tremendously excited by the growing number of available psychiatric drugs, mostly neuroleptics. Lithium had just made available; we were using imipramine, amitriptyline and Sinequan (doxepin), as the

* Carl Salzman was born in Brooklyn, New York in 1938.

primary antidepressants, with a little bit of MAO inhibitors, and Librium (chlordiazepoxide). Dick Shader was back at Mass Mental Health Center, having finished his NIMH training, and he, very much, insisted that I return and work with him after my two years at NIMH. Although, my wife and I had considered trying San Francisco, I couldn't resist an offer to return to Mass Mental Health Center. So back we went to Boston, which was home. I've been at the Mass Mental Health Center ever since. For the first ten years on the faculty, I worked as a colleague of Dick's, teaching psychopharmacology, helping him create a first-class psychopharmacology teaching program in a psychoanalytically oriented training program and collaborating on benzodiazepine research. At first, we conducted clinical trials, but Dick became interested in benzodiazepine pharmacokinetics and I became interested in geriatric psychopharmacology. At that time there was almost no psychopharmacology research or controlled clinical trials in geriatric patients or research in normal volunteer subjects.

RM: What provoked that interest?

CS: I don't actually remember, except that we had, in the course of one or two of our pharmacokinetic studies, a few older people and we realized that they responded differently. Dick and David Greenblatt were just getting interested in pharmacokinetics, and, the kinetics of some benzodiazepines, were different in the elderly from the adults. So, suddenly, I realized that geriatric psychopharmacology was like psychopharmacology had been ten years earlier. It was a new frontier. There was no information. It was incredibly exciting to be in the forefront of the field. So, we began to look at psychotropic drugs in the elderly and one of the things that became apparent is how much fun it was to work with older people, for if you had a good relationship with your older subjects they started to tell you about their lives. If you have any interest in history at all, you get history from people who lived at the turn of the century. And, in Massachusetts and New England, you get a fantastic survey of how the world has changed since the beginning of the 20th century. So a bonus, in addition to doing the research, I was getting to hear some amazing personal histories.

RM: You had to do a number of pieces in methods development.

CS: We did a lot of methods development and rating scale methods development, which was still in its infancy in geriatrics. We were doing the kinetic work, which clearly showed changes in oxidative metabolism in the elderly and prolonged half-life of drugs. And, dosing had to be individualized, and, generally lower. The pharmaceutical industry did not have any guidelines for giving drugs to the elderly. Basically, they said, use lower doses, which they still do, but we didn't have any precision about actual

necessary dose adjustments. Diagnosis of the elderly has fascinated me. In depression, e.g., the characteristics in over 80 year olds is quite different than in those between ages 65 and 80. Depression in the between 65 and 80 years old more resembles the depression in young middle aged adults than in the very elderly. In the over 80 year olds the chief characteristics of depression are irritability and withdrawal of social and interpersonal interest, as opposed to sadness, helplessness or vegetative signs. This may be even more relevant to the very elderly, over 100, who are now the fastest growing age group.

RM: Are there measures that people are using?

CS: Well, we're creating them right now. In fact, we're completing a double blind study of paroxetine, in over 80 year olds in a nursing home and one of the findings has more to do with the diagnostic discrimination of depression than with the patients' response. But, it's hard to make a clear-cut diagnosis of depression. When you ask some of the patients who are over 80 standard Hamilton Depression Scale questions, you realize that they all have sleep disturbance and they all feel relatively hopeless about long-term survival. If you ask an 85 year old how they think about the future, they will all say, what future; I might be dead tomorrow. But, when you ask them about social interests, and they say, well, I just don't feel like going and being with other people; I'd rather stay in my room that is one of the early signs of depression. And, irritability becomes worse with old age.

RM: When you look back as your work has evolved which individual or individuals do you think have made the greatest impact on your thinking in a sustained way? Part of it, obviously, is without mentorship, but there may have been some early mentors.

CS: Well, there are people that I always learn from and when I come to these ACNP meetings. I try to, either, talk with them or go to their presentations. I always feel like it's something new. You are one of them. Dick Shader was one of them, and, of course, Gerry Klerman was one of them. Jonathan Cole was also, but Jonathan doesn't come to to many meetings any longer.

RM: Jonathan Cole?

CS: Jonathan Cole. I almost always learn something useful from Ross Baldessarini. I almost always learn something useful from Charlie Nemeroff and Alan Schatzberg, who was a student of mine. You notice I'm identifying, primarily, clinical researchers, because I think it's important to clarify that I am a clinical researcher and teacher, rather than a basic science researcher, so the people that I tend to associate with do their work in the clinical area.

RM: It's really striking about your work the way you think about these issues. It's characterized by methodological rigor and an extraordinary degree of humanistic concern about people, and, you communicate both in your teaching.

CS: Well, I appreciate the comment.

RM: Well, it's true.

CS: I think that the one thing that always troubles me about the ACNP meeting when listening to the clinical research presentations is that there is not enough attention paid to real life human beings. It is almost as though the human beings are described as a collection of receptors or second messengers or gene expressions and other "neuroscience stuff" rather than suffering human beings. And, that makes sense if you're doing research. But taking the research results from these meetings back to the real-life clinical world, and, applying them to patients, requires a shift in understanding and application of the complexity of people's lives, because the diagnoses and treatment results are not as clear as it might appear when presented at these meetings. Depression is not just hypercortisolemia or what shows up on Hamilton's rating scales. That's not what depression is. And, yet, we sometimes think in simplistic ways because we're trying to understand basic disease mechanisms which may require temporarily reductionistic thinking. But I sometimes worry that, in our psychopharmacology research field, we are creating a generation of younger investigators who don't quite understand the clinical application or the complex realities of clinical treatment with these drugs.

RM: One of the things that you've really done in an extraordinary way in your educational programs, which you pioneered at the Mass Mental, has been to figure out ways to communicate the complexity by using case methods and other approaches.

CS: Well, I received a New York State research award given to me by Heinz Lehmann last week and Heinz is somebody who I would very much identify as a person worth emulating. What Heinz taught me, back when I was at NIMH, was the importance of being a good clinician. He taught me looking at the individual, as well as the whole body of data that might apply to the individual; looking at the patients and not just the mean changes on rating scale scores in the treatment research. One thing that Heinz could always tell, in a sensitive way, whether the patient was responding or not responding to the medication without rating scales and all kinds of fancy high tech stuff. And, of course, you were trained in that tradition, as I was, and Dick Shader, and Gerry Klerman and all the other Mass Mental Center residency graduates who went into research. The point that I'm leading up to is that to be a really good researcher, you have to be a

really good clinician. And, to be a really good teacher, you have to be a really good clinician and a really good researcher. The way to combine all three of those is using the case presentation method, in which you can take a patient and illustrate the larger research findings through implications and, then, also illustrate how the patient may not correspond to the specific findings of any research application, because patients, like all of us, are different. We're different from one another and we may respond in a "mean" way, but we also have "standard deviations", so to speak; we are individuals. And, that individuality brings teaching alive. That brings psychopharmacology alive and that's what we do at Mass Mental Health Center, and, if anything, I'd like to do more. If there was one area I would hope the ACNP might want to explore in its teaching role, as it did with the model curriculum, is creating a series of model teaching cases, based on real people, to illustrate some of the most exciting research areas that we're involved in right now, say, the new antipsychotics or the new mood stabilizers, the gene transcription potential theories, and, illustrate them through a patient.

RM: Do you see the potential through your own involvement over the next decade as trying to help to move the field in this direction?

CS: I see this next part of my career as almost exclusively doing that. I think that I will always be a clinician and always be a teacher and I'll always be a dabbler in psychopharmacology research, compared with most of my colleagues here. But what I really want to do is to try to bring what I learn here at the annual meeting back to the students that I teach and the community of clinicians and, to that end, I have, for the past almost 15 years, summarized the meetings. I sit down with my computer in my hotel room during the meeting and I type out the salient features of the abstracts or the presentations. I've gone to organize them by topic, and try to make them readable and understandable. If I can understand them, then, I think others can also understand them. And, then, I go home and distribute this note to the residents and the faculty. I hope to do more of that and, maybe, even expand it into the case base teaching method, as well.

RM: So many of your junior colleagues, who have been through the Mass Mental, identify you as the singular most important teacher and mentor that they had at the Mass Mental. One of the problems that we, as a field, face, but also all of medicine faces, is how to get people to recognize the importance of that mentorship role, and how do you generalize, from Carl Salzman to the larger community, to try to infect people with that enthusiasm, infect people with the importance of that piece of psychopharmacology.

CS: Well, you know, you've just given the answer to the question. You have to be enthusiastic yourself. You have to be a little bit lucky. I think I was lucky. I, you know, got to know people like you and the others at the Mass Mental Health Center, and was infected by their enthusiasm. Can you imagine Eric Kandel being a psychotherapy supervisor?

RM: It was incredible.

CS: With Gerry Klerman in the morning, we residents would talk about urinary catecholamines and then, in the evening, we'd go to his house, eat pizza and read Freud, with the same man. I mean, I wanted to be like him. I wanted to be like Dick Shader. I wanted to know all of this neurobiologic and psychoanalytic information and synthesize them together. I think you have to have the kind of enthusiasm that Gerry communicated daily. You have to really feel it and I think some people do and others have a passion in other areas, which they communicate. I think, without the passion, without the belief in it, it doesn't come across. Then, you have to find the willing student, somebody who's kind of interested but not sure and turn them on. If you can do one a year, it's a great gift.

RM: That's what happened to you in medical school. I mean, you really weren't interested in psychiatry at all.

CS: That's right.

RM: But, you got captured.

CS: I got, literally, turned on, as well as metaphorically. You know, there are many, many people at this meeting who trained with me, but the one who stands out as an example is Danny Weinberger, who was our chief resident in psychopharmacology. During his third year of residency, Danny had many talks with me and with others about what was he going to do with his career. I remember him standing at the door to my office; he was going to go to NIMH and I, basically, said, you know, Danny, find something that really excites you and just ride it as far as you can and your passion for it will keep you going and that's what you really want to do. And, he, very quickly, found schizophrenia and, my pleasure in having had a little bit to do with Danny's education and his career is endless. I just came from his session and it's just wonderful to see his passion continue to grow and provide us with exciting new discoveries.

RM: To APA meetings and here you would often bring young colleagues. You always push forward them to meet so and so and, then, so and so.

CS: Well, that, I learned from Al DiMascio. He brought me to my first scientific meeting, a CINP congress, and he made sure that I shook hands with everybody, knew which meetings to go to, have some fun and learn something. So, whenever I have funds and an interested student, I will bring them to the ACNP. I think Oakley got annoyed with me one year.

I brought 5 or 6 people to San Juan and, so, the rules about how many guests you could bring got tightened a little bit. But, I think that's the way to do it, and, of course, the ACNP is such a fantastic organization. If you bring someone who has any interest in psychopharmacology to one of these meetings, they're hooked. I mean, they say, "this is the best meeting I've ever attended", which it is. It is for me and that's why I do it for them.

RM: Let me refer you a bit back into the past. When you and Walter Pahnke became involved in hallucinogenic research, you had a very strong interest in looking at subjective states and so forth. Do you think that the whole issue of hallucinogenic research has petered out or do you think there is still some potential in it that people should be exploring?

CS: Wow, that's a great question! The answer to the latter question is definitely, yes. It, first, was a political problem. The drugs, of course, were misused and that became politically unacceptable. They also became scientifically unacceptable.

RM: Did you find that in your own early career?

CS: No, not at all, not at all. I still think that careful research into subjective experience, using these drugs would have a lot to offer to psychiatry, psychopharmacology, and students of brain function.

RM: What would it offer?

CS: Well, the kind of alteration of reality and subjective experience that these drugs can produce is unlike any that I or many others have ever experienced. It's not like being drunk or stoned or meditating or hypnotized and it's not like dreaming. Of course, we know these drugs affect serotonin function and they do produce some psychosis-like features. Although what they produce is really not a model psychosis, they produce a heightened awareness of one's own mental processes. The problem is, that it's very hard to study the experience and very hard to model it, because it is completely subjective. The term we used to use was "ineffable". That was one of the reasons I got very involved in the measurement of subjective experience and of placebo response. Some of the early work I did at the Mass Mental Health Center, and I still have some interest in it in my present work, is the understanding the subjective experience of different mood states, because except for vegetative and autonomic signs, they are subjective. How do you know when somebody is anxious? How do you know when you are anxious? I ask my patients, "how do you know you're anxious; how do you know you're depressed"? Then, if the descriptive words are more or less agreed upon, we more or less, understand each other, but it's always an inference.

Another problem with these drugs arose, and I really think neuroscience and academic researchers were a little bit to blame for this. It is characterized by a discussion I once had with Danny Freedman, another one of our great mentors and somebody who could synthesize all science and who also loved to philosophize, either at the ACNP or on long airplane trips. We were on an airplane from LA to Boston together, and while getting acquainted, we got into a discussion about hallucinogenic drugs; he was very much against researchers taking LSD. He said, “you don’t have to be psychotic to study schizophrenia and you don’t have to make yourself psychotic to study these drugs”. While I can’t disagree with that opinion, I’ve had that argument with him in my mind over the subsequent twenty years, even though he’s no longer here to argue with. He’s not right! It’s true, you don’t have to be schizophrenic to study schizophrenia, but if you are or have been or know somebody who is and you’ve seen the disease in all of its’ forms over twenty-four hours, week after week, you understand something about it that a psychiatrist or researcher who sees the individual in a brief cross sectional time frame, never gets. And, the same is true of subjective experience. The more you can personally understand what your research subjects or your patients are experiencing, I think the richer your research experience will be, the more informed your research questions will be and, ultimately, the better informed your teaching and clinical practice will be. Now, I’m not saying that everybody ought to take LSD, because those days are over, fortunately. But when we think about LSD, or any of the psychotomimetic as drugs whose only function is to kill serotonin cells, it’s as though we have literally thrown the baby out with the bathwater. To illustrate this: two years ago I was talking with a patient, who had come to see me, who had severe OCD. He was a wonderful bright 28 year old kid, who was crippled by his OCD. He really could do almost nothing and he’d been to many doctors because of his dysmorphophobic symptoms, rituals and other things. The one thing that made him feel normal was MDMA, “ecstasy”. He would get “ecstasy” on the street. He would take it and he would say, “for that hour, hour and a half or two, it wasn’t just that I was high or euphoric, but I felt normal, the obsessions, the compulsions, the worries that I have all vanished. And, then, they would come back”. Now, that’s an observation worth following up, but, of course, it’s hard to follow it up when you know that studying drugs of this class is going to kill serotonin cells and no ethics committee going to let you do it. And how are you going to find subjects if you’re not going to take it yourself. And, if you generalize this conundrum to the whole scientific field, it becomes very difficult to study the alteration of subjective experience with any chemical that doesn’t have clear

- therapeutic value. After all, we don't advocate people becoming alcoholics in order to study alcoholism.
- RM: Yes, but what you're suggesting is that we are missing an entire area of drug discovery, and, if we had an ecstasy that didn't kill serotonin cells, that would be a very important redirection for drug discovery.
- CS: Yes, and I'm saying not only that, but I think we have all become frightened, both, by the political, as well as the potential neurotoxic consequences of these drugs and, so, we have abandoned an area of psychopharmacology research, which I think is potentially, clinically, amazingly rich. And that's sad.
- RM: In a sense, Timothy Leary has met Aristotle. But, you're telling us to rediscover William James?
- CS: Actually, well, that's absolutely true; to rediscover the original Timothy Leary before he became a showman. When I knew him in '61 at Harvard, he was not the way most people now think of him. He was a careful, sober, scientific thinker, who was really interested in the alteration of subjective experience and the psychological therapeutic properties of these drugs. It was only later that it all went in a different direction. Sad!
- RM: There's another piece that people who don't have your solidity, got, caught up in. And, that was that you did with Richard Katz and Walter Pahnke in which you discovered the capacity of hallucinogenic drugs to produce shared subjective experience. That was really profound.
- CS: Oh, that's another whole interview.
- RM: I'm sorry.
- CS: It's a terrific subject so..But you're absolutely right and, of course, it was poisoned science. It was anti-science; it was anti-intellectual. Ultimately, that's why I didn't continue in this area of research and, basically, severed all my ties with Leary although I did call him before he died.
- RM: You did?
- CS: I did. I hadn't spoken to him in twenty-five years but we chatted on the phone and I said goodbye to him. I reminded him of how important role he had played in my life. He wasn't too interested in my being a psychiatrist, but he was very cordial and very friendly. He was dying.
- RM: That's remarkable.
- CS: Yes.
- RM: Do you feel any disappointment that that part of your work was not really continued?
- CS: No, I don't, Roger. I've had a very rich life. I've had a terrific professional career. I think I'm really enjoying now the benefits of the years of hard work and I feel very good about it. My regrets are not in that area at all. My regrets are, perhaps, more in the area of not having been a good

enough, scientist and devoted more of my time to research, but I had so much interest in the clinical and the teaching area that I couldn't do it all.

RM: Yes, but you also decided early on where your passion was. Then, you followed your passion just as you told others to follow their passion and you didn't force people to be a Carl Salzman. You really forced a Danny Weinberger to be a Danny Weinberger. That is a remarkable quality for a mentor.

CS: Well, thank you. I never felt in competition with my students. In fact, the better they did, the happier I was. Just as a personal note, all of my family were teachers. My father was a teacher and I remember him saying to me, once, you can do anything you want, but "don't be a teacher"! So, here I am, a teacher.

RM: What do you think about the Mass Mental? It was a great spawning ground of so many really outstanding scholars and scientists and, yet, the environment that you were trained in, it was very psychoanalytically based.

CS: Well, it was psychoanalytically based, but, again, it was a place of superior people, rather than just superior theories or monotheistic theories. If you think of the many people who were there and their enormous range of interests, it was like being in a university for me. It was possible to become involved in psychoanalytic psychology. It was possible to become involved in interpersonal and behavioral programs. It was possible to be a basic scientist researcher with the animal models of sleep, of affective disorders and, even, of schizophrenia. It was possible to be a pharmacologist and a psychopharmacologist.

RM: But, in your class of, say, 24 residents, there were you and Herb Meltzer. Who else went into psychopharmacology?

CS: Bob DuPont, myself, Ed Khantzia, and Herb, of course, is the preeminent alumni of our training group. I think that's all for psychopharmacology.

RM: So that it took a certain passion, as you had, to follow the psychopharmacology.

CS: That's true, but, if you recall, there was always a minority of people at that time who were interested in research and particularly interested in biologic research, and they almost always went to NIH. Remember, the shuttle bus between Mass Mental and NIH, and the Tuesday lunches where we would talk about the "old days at Mass Mental" and the new days in psychiatry yet to come. That was a very select group of people and I felt privileged and honored to be among them. The Mass Mental alumni, who populated NIMH on the campus as well as off the campus at St. Elizabeths Hospital, were fantastic people, and to be among them, I think, was the high point of my life. To be at Mass Mental and among

those people, I think was clearly something that I had never thought of that it would happen and, now, looking back, it is unquestionably the high point of my professional life.

RM: And, as you look over the history of the Mass Mental post 1960, you are the singular institutional memory.

CS: I am, I'm the one carrying the institutional memory.

RM: You're the one who can really identify it through to the point where it is now and that's an incredibly singular and significant role in American psychiatry.

CS: Well, I loved it. It now feels a little lonely, but you know, it was a special place with special memories.

RM: It's a very special role.

CS: Of course, people like you and I also have a memory of the ACNP, because it goes back thirty years, now, in watching the organization evolve and change and how it's worked out and that feels good, too. I must say, I feel very fond of this organization. The annual meeting is, unquestionably, the best meeting of the year.

RM: Yes. Is there some major question that I didn't ask you that you really would have loved to have an answer to?

CS: I thought you were going to ask me what I thought about the organization and how it's developed and what's good and what's not so good, some of the things we've talked about at our "annual beach" talk. I've given a lot of thought to those things and I don't know the answer. I'm also afraid that my comments are going to be misunderstood, so I have to be careful in how I phrase them. I have very mixed feelings about the relationship between our organization and the pharmaceutical industry. On the one hand, industry certainly supports many scientific activities. And, I also think that the meeting between the academic research community and the pharmaceutical research community is a tremendous area of cross pollination and fertilization that has led to great discoveries; I think it would be nihilistic and cynical to say otherwise. But, I think there's another side to it. I think we are all, including me, too influenced by industry in sometimes very subtle ways. It's rarely vulgar: nobody from industry ever says, "say this and don't say that" about our product. That would never happen, but the influence is much more subtle in terms of how we understand the clinical application of drugs, how we compare drugs and how we gather the data and present the data. You can see it here at the meeting. If you look at some of the posters in which studies of drug comparisons or drugs vs. placebo are presented, you know that the study is, in part, been funded by industry. You know it because you already are familiar with the work, so you have some basis of judgment. And you can

see that there are statements that are not made, and information that is not presented, so there are data errors by omission. It's not necessarily lying, but there's subtle inference given that this particular drug is, say, better than that particular other drug for these particular patients, and here are the data., When you have had some experience with the drugs, or carefully examine the methodology, you say to yourself, "that's really not true". So it requires in all of us, a need to maintain a high level of scientific and clinical rigor in evaluating drug company data, because what we learn here at the meetings may, in fact, not always be, in fact, applicable or correct in the clinical world.

RM: You know, you just did a remarkable thing. I was thinking about it. You've benefited from industry support, your education programs, your research that you've done. You recognize the value of, what's been called the triangle, the powerful triangular relationship of academia, industry and government. It's like the way that you've described the LSD and hallucinogenic drug potential for good and the ways in which it got carried away by due process. Your argument, basically, is to recognize the good, but don't become carried away by forces that subvert your own judgment. In that thinking, in the way that you described the dangers, as well as the benefits of the relationship, you also reaffirmed the Carl Salzman approach to the work, which is retain your individual groundedness; don't get carried away by movements and really stay the course in the set of very good principles.

CS: OK, you said that in such a nice way. Remember, in my work at NIMH with Jonathan Cole, I was running the ECDEU program, and as Jonathan originally created it there were no drug company people who participated in the investigators meetings. It was a small group of very gifted and sensitive investigators, who met several times a year to discuss their work without fear of interference or the consequences of what they were going to say, from industry. I don't think that's possible to do any more. The world was different then with fewer drugs and a smaller number of investigators; it was very special time. And, the discussions around those tables changed when there were drug company people in the room. I saw it with my own eyes. I wouldn't say scientific rigor hanged, but the level of openness changed; hard questions would not get asked when industry reps were in the room, because you might be stepping on somebody's company toes or because there might be financial or professional repercussions later on. Again, I want to emphasize that I don't think only "the good old days" are the only good days, but there has been something a little bit lost. I was wondering, in preparation for this interview, what would I want to do? I made a comment to the FDA Advisory Committee last Thursday, which I think would apply here, as well. We

were discussing a post marketing survey of side effects at this advisory committee meeting, and the question of how do you get good, reliable and valid information about side effects, once a drug is out? Mainly, if it's not lethal and doesn't make the media, you get it from what the industry collects, as well as from spontaneous reporting to FDA. And, it occurred to me that we should resurrect the old ECDEU model. We should have, say, 10 or 12 designated gifted clinicians, Heinz Lehmann type people, from around the country, who observed the drugs in their clinical use, monitored the emerging side effects and, then, came together to discuss and compare and share observations. Did you see sexual dysfunction with SSRI's? Did you see weight gain with the new generation of antipsychotics? Those kind of discussions would provide a very effective early warning system. Taking that model and bringing it into ACNP would mean to have a small group of designated clinical researchers or, even, basic scientist researchers, meet, informally, maybe three times a year, maybe in conjunction with this meeting, to discuss amongst themselves, what they've observed, and the clinical implications of their research. The information shouldn't become public, but the scientific community could then be informed about it without the influence of the industry. It might not be expensive and it might be practical.

- RM: Do you know if the practice network that the APA is sponsoring is doing any of this?
- CS: I don't know, Roger, but the other side of it is that the information, now, that we developed gets out on the internet in incorrect ways and, so, if anything, we're in a much worse position, in terms of misinformation or mischievous information, being disseminated than before. And, it would be nice to have a group of people meeting, who were not under any influence and could just look very hard at the data and their implications. After all, it's the implications of what we do that's important. I mean, we need to learn things for their own sake, but we're basically an organization of doctors, who want to help people.
- RM: So, one of the functions that the ACNP could have in the future would be to try to foster this kind of unrestricted, uninfluenced research discussion.
- CS: Right, and I'm concerned that the new society, the American Society of Clinical Psychopharmacology, grew up because the ACNP wasn't doing enough of this clinical work and I think that's regrettable. We need to keep the rigor in our work and that's what I think the ACNP does, to its' credit, but it has somehow abandoned a little bit of rigor on its' more clinical side, and that's reflected in these annual meetings
- RM: What's been the impact of managed care in clinical psychopharmacology, as you've seen it?

CS: Well, there was a poster last night on the Treatment of Depression in Managed Care in Ten Thousand Patients, in which Sertraline vs. Treatment As Usual was studied, and compared with a special algorithm. People treated As Usual fared better.. But what is distressing is that the special algorithm was administered by non-psychiatrists. So, what is happening, of course, is that many of our drugs are now being routinely prescribed by non-psychiatrists, which I suppose is not bad from a public health point of view if the drugs are used correctly. But, it certainly is marginalizing clinical psychiatry to take care of only the treatment resistant and the more complicated patient and the co-morbid conditions. I don't know whether that's good or bad, but basically I think it's bad.

RM: Where did that study come from?

CS: There were four managed care networks that collaborated. One was funded by Pfizer, because the government wouldn't fund it. I think, what's happening, is that psychopharmacology practice is being influenced by managed care pharmacoeconomics. Clinical observations, which then follow the pharmacoeconomics may not be accurate, but look accurate, because you have these large "N's" and you've phrased your questions in such a way that it looks like this algorithm, in fact, works. Well, that was a very easy study to criticize; it was a terrible study and none of us would have accepted it for a journal; they didn't ask the right questions and they didn't really have the right controls and they didn't really provide the right answers. But, they got Hamilton ratings. And depression is more than Hamilton ratings. But, that's one of the major influences of managed care and these large scale survey studies. Another major influence, of course, is that it's almost impossible to do inpatient research in community hospitals. And, of course, it's also almost impossible to find outpatient volunteers, because the managed care company would not let them participate unless they kind of sign wavers and say they're not going to get care through the managed care system. It's very worrisome. It's worrisome in teaching, too. All medical schools are finding very hard to teach psychiatry and the treatment of the seriously ill patient in managed care settings, because they are managing people, not really treating people. It's very different from the psychiatry that we learned at Mass Mental Health Center.

RM: We've certainly reviewed the history of ACNP, Mass Mental and Psychiatry and it is clear that you will continue to influence the next decade and more trainees.

CS: Well, thank you, Roger.

RM: Thank you.

RICHARD I. SHADER

**Interviewed by Carl Salzman
Medford, Massachusetts, March 24, 2008**

- CS: Good morning. I'm Carl Salzman. This is March 24, 2008. I'm talking from Tufts University School of Medicine and I am here to conduct an ACNP interview with Dr. Richard Shader,* a distinguished member of our college and a world renowned psychopharmacologist. Dick, good morning!
- RS: It's a pleasure to be here with you, Carl. We don't get a chance to talk very often these days.
- CS: Dick and I have known each other for more than forty years. Dick was my mentor, my teacher, my colleague and close friend and we have a lot of stories we share in common and I'm going to ask Dick about some of them. But, Dick, let's just start by talking about how you got to Mass Mental Health Center and, then, we'll pick up from there with your career.
- RS: Well, I was born in New York, actually in Mount Vernon, just outside the City, and my family was there during the Depression. They were struggling down in Florida, where they had lived before. It was hard to make ends meet and they came up there to find work and, then, after a few years went back. Shortly after going back, I entered the public school system in Florida and that was my life. I went through the schools there, came up to Harvard, became very interested in research, became very interested in psychiatry, in large measure because my dad had struggled with depression. I wanted to understand what one had to do to conquer his problem. I still wonder about what it takes to conquer this problem many years later. And, after medical school at New York University I came back to Boston to Mass Mental and that's where we met after I had come back from a 2-year stint at the NIH.
- CS: Tell us a little bit about your residency and, then, getting to NIH, your work with Jack Durell there and, then, coming back.
- CS: Well, the residency was in a very exciting time; back in the very early 1960s. Mass Mental was very much in its heydays, accepting large numbers of residents. I think there were as many as 24 residents for some years and the group was divided in terms of interests. There were those who were interested in biological psychiatry; those who were interested in psychoanalysis, and some of us who were interested in both. And, depending upon what camp you were in, you felt more or less comfortable there at various points in time. It was a place that was, I thought,

* Richard I. Shader was born in Mont Vernon, New York in 1935.

renowned for being at the cutting edge at that particular time. I had a year there in 1961 when the Berlin crisis was going strong, and the government called me to active military service. Fortunately I was able to secure a commission in the US Public Health Service and, even more fortunately, I was able to be stationed at the NIH. I went, at first to Seymour Kety's laboratory and, then, was assigned through Seymour Kety's lab to Jack Durell where we worked on some very interesting projects related to early onset schizophrenia and many of the determinants of it. We were also interested in periodic psychosis and whether they were very specific determinants of periodic psychosis. As I recall, we were very interested in the work of a Scandinavian psychiatrist named Gjessing, who studied periodic catatonia. And the project that I worked on had two parts to it. One part was to look at the role of the thyroid and whether you could predict episodic changes in thyroid function and, indeed, it looked like you could. Nothing ever happened with that work. Ever since then, people still argue as to whether periodic catatonia is an entity that exists or not. But, the second thing that I worked on, which was very interesting, gave me an introduction to working on scales. We developed a rating scale at that time for social functioning after one recovered from psychosis. It was a very elaborate scale, but, again, nothing came of it after it was published. Quite interestingly, lots of scales have been developed since then to look at quality of life and, to my knowledge, ours was the first major quality of life scale around, which we used in our studies and published in our reports.

CS: So, then, from NIMH, you came back?

RS: Came back to Mass Mental to finish my residency, yes.

CS: And, what year was that?

RS: That would have been 1964, which was just when you were a first year resident.

CS: And, who were your mentors and how did you get involved in psychopharmacology at Mass Mental?

RS: Well, I was interested in psychopharmacology actually before coming to Mass Mental. I had worked during college on the artificial kidney that was being developed at the Peter Bent Brigham Hospital, now known as Brigham and Women's Hospital, and in that work we saw a number of people with mood disorders. So, when I thought about the difference between some of those people and what I used to see in my father, who had episodes that seemed to come out of the blue, and after he recovered had long intervals of good functioning in between two episodes, I began to be intrigued by the biology of mood shifts; how much was in one's genes, how much was related to stress, how those things kind of

interacted and how could they be modified. ECT was around, but I would see some people recover by themselves, and other people who seemed to be very chronically depressed. So, I went to Mass Mental Health Center, very much committed to biological psychiatry already because I didn't think that you could talk people out of serious illness. So, I felt we needed to have medicines to do that. Even so, I felt you could make a great impact on helping people to understand themselves better, particularly people who had the time and inclination to do psychotherapy.

CS: Let's just touch upon some of the people who were at Mass Mental at the time, like Milt Greenblatt, Gerry Klerman and Eric Kandel.

RS: They were all there. Eric was a resident. He was a year ahead of me; so, not a mentor, but he was certainly a friend and colleague. Gerry had just come back. He had done his training and was very much a junior faculty member at that point, a very brilliant man. He was probably the only person I ever encountered who had knowledge about what was known biologically and, at the same time could cast things in terms of the psychological theories of psychosis; he was able to frame a history how it might have been interpreted by Freud, how it might have been interpreted by Adler, etc. Although, he was very committed to biological psychiatry, he was also a very comprehensive teacher and through his comprehensive approach, he fostered my more pluralistic thinking at the time. Milt was very much a personal mentor to me, even if not as much a science-mentor. He was very much involved in the development of the grants that we had to run our clinical research center for schizophrenia and very involved in some of the grants that we had for affective disorders. I, essentially, became his research assistant and he was sort of a father away from home for me. We made a pact that Milt would look after me and then when David, his son, would get a little bit older I would begin to look after David if he chose to go into medicine. And, we've been together for some forty years. It's been a very productive and special relationship.

CS: And, were there other leaders in biological psychiatry at Mass Mental at the time? I'm thinking of Max Rinkel and Bob Hyde.

RS: Bob Hyde was around and I knew Bob, not only through Mass Mental, but through Al DiMascio, who had been a colleague of his, and was certainly an early person who was important in the teaching of psychopharmacology at Mass Mental Health Center. So, I knew Bob, but I didn't work directly with him on any of his LSD work. Bob had also been a colleague of my psychiatrist brother-in-law, Arnie Abrams, so I knew him in that way as well, but I never knew Max to any extent. Ed Sacher was also a resident, so there were a number of other people who later went

on to move the whole field ahead, but not people who, at that time, were heavily involved in research.

CS: Just before we move on, I don't want it to go unnoticed that at Mass Mental Health Center you worked on what was called the CRC, a schizophrenia research ward, and you co-authored the book, *Treatment of Schizophrenia*. Could you comment about that research program?

RS: Well, that was a fun program. As you know yourself, we had this very small ward with extremely chronic people and the idea at the time was to demonstrate the value of psychotherapy and to see its' relative merits vs. pharmacotherapy because there was tremendous skepticism at the time about the role of antipsychotic agents. At those times, we called them neuroleptics and we were very committed to trying to see what the interplay was among the various interventions that were made within the dynamic milieu of a ward. These were people who were very sick and, I know, because I ran into some of them in later years, they remained very sick, despite all the interventions that people made. But, it was a very interesting time and one of the projects that I worked on myself, which I thought was probably the most intriguing for me, was how to do a controlled study and whether you needed to blind everybody or whether blinding would be broken by side effects. So, one of my earliest and most significant published pieces of research, early on was about the development of an active placebo. You may recall that we mixed phenobarbital and atropine in doses low enough to give a little bit of dry mouth and a little bit of sedation so the staff couldn't tell the combination apart from the active drug; but you could certainly tell by who responded to what, who was on active medication and who was not.

CS: And, Herb Meltzer worked also on that unit?

RS: Yes, Herb came later. Herb came to MMHC along with you at the same time that I came back from NIH and he took over as Chief Resident on that unit.

CS: So, how did you then move from that position into the psychopharmacology program, which Gerry Klerman had started?

RS: Actually, through Al DiMascio. Al was a psychologist and there were issues at the time about psychologists being PI's on grants that involved medication. We had long discussions and I had consulted with him and worked with him and helped write a draft of a grant for him. And, then, it turned out that if we were going to keep this medication research going and move it forward, it made more sense for me to be the PI of the grant than it did for him. So, as a result of that, I took that over at about the same time that Gerry Klerman was getting ready to move to the newly built Lindeman Mental Health Center. So, by those coincidences of time

and where I was particularly positioned at that moment, I took over the psychopharmacology program and actually expanded it, because it had been quite small up until then.

- CS: That's just what I want to get to, and I want to be sure that we capture the excitement of the emerging biological and psychopharmacology research within the background substrate of psychoanalysis, which you, yourself, was trained in, which made you rather unique.
- RS: Well, Gerry was trained in it for awhile and Ed Sacher was trained in it for awhile. They didn't complete their training, but I did and it certainly made one try to clarify the distinctions between being unhappy and being depressed, being stressed and falling apart.
- CS: You often taught me that it had an effect on their research questions that they had a good clinical background.
- RS: Yes, and one of the distresses I have about today's research is that the patient populations are so mixed and confusing that when we don't really find what we think we might find, you never know whether it's the patient population or the design or the medicine or how we're to interpret what we do or don't find.
- CS: Okay, now, among the exciting people that you were working with was Al DiMascio. So, could you just say a word for the oral history project about Al and what he was like?
- RS: Al was a delightful, high-energy person. That's the way I think of him. He was the first and only person I knew personally who drove a Corvette. Sadly, he died driving that Corvette. But, he was a promoter. He was working on his PhD, actually, when I knew him and finished it during the period of time that we were working together. And, interestingly, he got his PhD on the topic of What Stress Did to Dental Decay in Rats. We got interested in a topic that I have stayed with my whole career, which was "What Are the Factors that Influence an Individual's Response to a Medication", and, at that time, we were interested in personality factors. One of the very first things we did was to look at a very simple dichotomy: If you got a cold, did you want to stay in bed or did you want to fight it? And, interestingly enough, as you know, we found that people who like to stay in bed seemed to like Valium (diazepam). People who didn't like to stay in bed when they got a cold couldn't stand taking it. This was essentially in healthy volunteers. We began a healthy volunteer unit that was at the time, part of an effort of the psychopharmacology research branch. Before NCDEU, it was called ECDEU (Early Clinical Drug Evaluation Units), and we were the one Early Clinical Drug Evaluation Units that worked with normal volunteers; so it was very exciting. And, as you know, that work evolved. When you came into it the work was on paradoxical rage;

whether or not you could predict who would become angry and hostile, instead of being calmed, after the administration of a benzodiazepine.

CS: This research led to making your program a center for benzodiazepine research and it also moved the benzodiazepine field forward. Could you comment on that and, maybe, reflect on what's happened with benzodiazepines over the years?

RS: A very controversial subject. Well, we were very interested in, again, who responded to each various medications and how. Some of the work we did when we began to have the capacity to do things like pharmacokinetics and blood levels, grew out from this interest when David Greenblatt got involved with us. He had just finished the earlier part of his training in Internal Medicine and was interested in Clinical Pharmacology. So David joined us and began to do the work that allowed us to look at concentration relationships to behaviors and not just to dose and to try to be much more specific about it. So, what happened there? Well, we used to do a lot of this work with ourselves as our subjects, and we discovered that I could take 100 mg of chlordiazepoxide or Librium as it is known, intravenously, and it wouldn't touch me, whereas David would fall asleep after he took 50 mg. So, we began to try to understand more about individual differences in drug response first in normal subjects, and, that was a way for us to get into more general pharmacology. Using what we learned about kinetics became ways to study all kinds of drugs, not just CNS drugs. But, as you know much of clinical pharmacology grew out of from early work with CNS drugs, followed by work with cardiac drugs. And, then, when those two expanded, we had a much broader knowledge.

CS: What's interesting to me, Dick, is here we are forty years later, and the pharmacology and pharmacokinetics of benzodiazepines are still the best known of all the psychotropic medications.

RS: Well, fortunately, the NIH at that time had the resources to invest in allowing us to find those things out. But, you know, the controversy developed when questions got raised about the addiction potential. We noticed that there were many people who took the drugs and had no problem at all and, then, there were a small subset who did seem to have some problems that again raised questions of individual differences. We got interested in partitioning whether obesity and fat made a difference in what got into brain, and what got into the rest of the compartments in the body. We got interested in the differences between men and women, so it opened many doors to look at factors that influenced response. As you know, the Church of Scientology got very involved at the same time that we got involved, a little bit later, actually, and what their motivation was I'm not absolutely sure, but they certainly put a lot of resources into trying

to discredit the value of these drugs. And, I think with the publication of such books such as *I m Dancing As Fast As I Can*, benzodiazepines got a very bad rap. That bad rap was not deserved, because there was an equally good amount of research and really good research to show that the majority of people who took these drugs took them safely and didn't become tolerant. In fact, if anything, they would lower their doses over time so there wasn't a whole lot to support for the notion that these drugs were dangerous or as dangerous as they were being made out to be. But, I think that, you know, the public is always looking for controversy and this was a good controversy for people to sink their teeth in, particularly since it was financially being fuelled by a group that had a big investment in seeing that the public recognized it as dangerous. And, it took many years before the World Health Organization reversed itself. They initially came out with a statement that these drugs basically should not be used and, then twenty years later, came out with a statement that, for what they were intended to accomplish, they were probably the best and safest things we had available. The woman who wrote *I m Dancing As Fast As I Can* retracted her statements that Valium caused her problems, but nobody paid attention to the retraction. People, usually, only pay attention to the first and most controversial part. So, there's still a lot of business in this area. You see, people advertising drugs that work at the benzodiazepine receptor as non-benzodiazepines as a way of making a point and sort of staying away from that area.

- CS: It's still a problem getting young doctors to understand that these are safe drugs.
- RS: Absolutely.
- CS: Before we continue on with the development of your career, I want to be sure to mention another aspect of your pioneering work, and that was the beginning of geriatric psychopharmacology. Perhaps you could just recall some of that. It was going on at the same time of the benzodiazepine work and, in fact, they were mixing together.
- RS: Well, we did get very interested in age as a variable and we got particularly interested because we also felt that one place that benzodiazepines were being misused was, perhaps, in some nursing homes as a way of keeping people quiet and not because they were necessarily anxious. We became interested in the positive value of these drugs for the elderly, and also why they might be more sensitive to them or not sensitive to them. But, certainly age as a variable became a very important part of wanting to understand individual differences.
- CS: As we all know, there is a lot of controversy about the role of drug companies influencing the outcome of research and there's an anecdote that

has stayed with me for my whole life and I keep on repeating it to young students, now. You and I did a study of a geriatric drug that was supposed to be good for memory; it was compared with imipramine and when we finished analyzing the data the drug turned out to be worse than imipramine. And we wanted to publish it; you wanted to publish it, and the drug company said, no. And, I don't remember whether you recall what you did, but I recall what you did.

RS: Please refresh me.

CS: You threw the drug company representatives out of the hospital and told them never to come back and that you would never do any research with that company again.

RS: My goodness!

CS: And, it was a great moment for me and one, which I think we all should acknowledge and observe, because it was the right thing to do.

RS: Did we publish the paper?

CS: No, we never did publish.

RS: And, that's the interesting thing about drug company sponsored research; the ownership of the data. Today, it would be quite different. Today, that would not happen.

CS: Okay, now moving along, the kinetic work was growing along with your interest in general pharmacology. You were also teaching at Mass Mental Health Center. This was before 1979, and I do want to emphasize your brilliance as a teacher. You and I did a lot of teaching together, but you really created a lot of the program and actually were the Residency Director for awhile.

Do you have any memories or reflections of that?

RS: Just that it was fun. These were very halcyon days, even, if at the same time, the Halcion controversy was going on, but, you know, those were great days. People were interested in learning. People did not seem to shrug having to read something as they now do. They had more time and there was much more investment in the educating trainees than I think is often the case now where you learn by doing and not so much by spending time with mentors. They were days when people were trying to understand what's happening and what's not happening and why and why not. So, those were very interesting times and I think that teaching was fun.

CS: And, that led you to accept the position here at Tufts in 1979, and leave the Mass Mental Health Center. It led for us to go our separate ways, which was for me a very difficult decision. So, you came here and started in the psychiatry department and, then, moved to pharmacology. Could you talk about some of your work in pharmacology and psychopharmacology as you came over here?

RS: You made the wise choice, I think, for your own development, not to join us over here. Well, when I got here, there were a lot of administrative duties, initially. Then, David came along, which I think was a very good choice for him, and we were able to expand our laboratory capacity and to evolve into being able to do much more research than we would have been able to do at Mass Mental Health Center. But, the role of being a Chairman was a very time consuming one, in terms of administrative duties related to fund raising, related to public relations, related to getting along with other departments. In fact, it's a very different being in a general hospital setting than it is in a psychiatric setting, much more enriching in many ways, because you see different patient populations. But the job was really to keep the place going and make it grow and expand. We were able to move beyond, an almost exclusively psychodynamically oriented department that I inherited from a very able man, who had actually been one of my psychoanalytic teachers, the late Paul Myerson, whom I had tremendous respect for, but there was a narrowness in the educational activities here. So, expanding into a more pluralistic program and having residents understand that you couldn't give pills to people without talking to them and expect good outcomes was very much a challenge and one that I enjoyed taking on. But, we were also able to expand the research at the time and we had great success with our grants at the time. And, 1989 was the year that I really began to feel that I had done enough of being Chairman of the Psychiatry department. I had another mentor here, who was Lou Lasagna, who, as you know, was a President of the ACNP, and who became a very close friend of mine. And there was an opportunity to remake the Department of Pharmacology here, which had been part of Biochemistry as one department, Biochemistry and Pharmacology. So, in 1989, I accepted a position as Professor of Pharmacology and begin to think about and expand the department. Then, as you may recall, in 1990, I had my bypass surgery and I went on sabbatical for a year, to the Center for Advanced Studies in Behavioral Sciences, now part of Stanford. I worked on my interest in anxiety there, and on the relationship of worry about the future vs. worry about the past in areas of omission and commission and suggestibility. All of that came at a time when I had a great deal of time to think about it. And, when I came back, it had been decided, to formally split the departments of Pharmacology and Biochemistry, and I became the first formal Chair of the Pharmacology Department, which I did for two and a half or three years. By then, it became very clear to me that I was running out of gas, as far as administration was concerned, and, I wanted to get back to doing work in research and expand my teaching.

CS: There was an irony that you probably don't know about or may have heard, but at the moment you were having a bypass surgery, Ermino Costa was giving the ACNP Al DiMascio lecture at Tufts. He noted that we were all sitting in the audience, feeling quite upset and anxious and he looked at us and said, I had a bypass, and, now, look at me. Dick will be fine; don't worry about it.

RS: That, I didn't know. You know so many things about me that I don't know.

CS: And somewhere in there, Dick, you also increased your activities in the ACNP and, ultimately, became its President.

RS: Yes, that was at the same time, actually. Before becoming President, I was President Elect and Vice President; a position, I'm sorry we don't have anymore. When I was Vice President, Gerry Klerman was going to be the President. And Gerry died; a tragic loss, a very fine man. So, after having served as Vice President, they decided to do away with that office. And, then, I became President elect. And, then, the year of my presidency was actually the year of my bypass surgery.

CS: Could you comment on how you saw the ACNP as you were leading up to your presidency and, then, what there was during your presidency that you thought was important?

RS: Well, I always thought it was a terrific organization. Again, I was very lucky in that through Seymour Kety, who I worked with at the NIH, from 1962 to '64, and Al, who were active in the ACNP, I actually went to my first ACNP meeting while I was at the NIH. And then, I became a member very quickly, much to my delight, because, as a small meeting, it was probably the very best place to learn through the workshops and through the close contact that people had with each other, about the interaction of mind and body, about drugs, about drug design, about everything you might want to know about psychopharmacology. Over the years the organization became more political, which I was certainly strongly supportive of, and we began to lobby actively, lobby for the Decade of the Brain, lobby for the appropriations for the NIH. We worked with issues having to do with advocacy groups. We got very involved in promoting advocacy groups at the time and I would say that the highlight for me was, in fact, the year of my presidency when the Secretary of Health and Human Services, Louis Sullivan, came to our meeting.

CS: I remember.

RS: And, that took over a year of very hard work and preparation. It was an acknowledgement of the role of the society as a group of scientists, who could make positive contributions to government decisions. But, then, I think there were many members who felt we went too far and that we had become too involved in the political process. And, we seemed to pull back, at that point, as a group. And, there was a movement during

my presidency from the American Psychological Association to give prescribing privileges to psychologists who were in the Army because of an MD shortage. I did not see that as a solution to a very real need and was very actively involved in trying to make sure that what was done was done so that no one was put in jeopardy, by trying to insure that all the psychologists who would get prescribing privileges go through a very rigorous kind of education in his psychopharmacology training. Since then, of course, as you know, lots of people have prescribing privileges now with much less education than the trained psychologists did. I have mixed feelings about it. I'm not at peace about that, myself.

- CS: In a very curious way, in a course that I was teaching, just two weeks ago, one of those psychologist trainees who took that course told me that she had learned psychopharmacology under the auspices of the ACNP, and that she was tested to make sure that she knew enough. That was interesting.
- RS: Yes, it is. I don't have a long term follow up, so I don't know what's become of the program.
- CS: So, you really became a pharmacologist, not just a psychopharmacologist, and that expanded your horizon and your view. Could you comment upon that new career direction?
- RS: Well, some of it was born out of necessity. When I took over the Department of Pharmacology and Experimental Therapeutics it became very clear it wasn't large enough for everybody to be able to do both research and teaching and everything else academic. We had to move things forward in a quick way because we wanted to grow as a department. And, at that point, I began to do more teaching to relieve some of the faculty of teaching responsibilities so that they could get more RO1's, which was going to be their survival and the survival of the department. To do more teaching I had to do a lot of studying and that was fun for me. I was getting a new education, mastering a new body of information and was trying to translate it to people. And, sometimes, that was successful and sometimes it wasn't, but it certainly all along has been an interesting time for me.
- CS: Now, as part of this, you were always writing, always publishing and you also started a journal. We want to be sure to mention that and how did you come to decide to do that?
- RS: Well, that was at Mass Mental. In 1978, we began to talk about the curriculum for residents and how we were going to educate psychiatric residents. My feeling at the time was that we really didn't have a journal that would bring clinical psychopharmacology into the foreground. There was a wonderful journal, *Psychopharmacology*, which existed at the time, but it primarily focused on animal work and on animal models and there wasn't

a place in it for clinical research As you know, just to back up a step, I was very interested in drug side effects and did that book on drug side effects. I was very interested in the complications of drugs that affected other organ systems, which is really where my general pharmacology interests grew from, the medical complications of psychiatric drugs. When we were thinking about all that it made sense to see what would happen if we could create a journal for clinical psychopharmacologists that would bring all this kind of information together in one place. So, we went to a number of different publishers and nobody thought this was a very good idea at the time. But, fortunately, Williams and Wilkins thought it was a good idea and were willing to back it and get it started. Later, the ACNP came along with its' own journal. We tried to talk the ACNP into doing it in the beginning, without much success. I'm glad that they have come along later with their journal, as well, because it's another contribution to learning. But, that was basically how it got started. We are now twenty eight years later and the Journal is still going strong. It's a great journal.

CS: Okay, what about medical complications?

RS: You're reminding me about my book.. Yes, well, I find it very interesting to go back and look at that book on *Psychotropic Drug Side Effects* from time to time, because, particularly right now, there is all this fuss, an appropriate fuss, about the "metabolic syndrome". Mike Ebert and I wrote a chapter in that book on glucose metabolism, the effects of drugs on glucose metabolism and actually everything that people are now saying is right there in the book but no one ever quotes the book, because they don't know it exists. But, what was very interesting to me, when I go back and look at it was that we uncovered work in that area by people like Frank Braceland, who was head of the Hartford Retreat, and who had been one of the earlier presidents of the American Psychiatric Association. He studied the glucose metabolism of schizophrenics and found out that they, basically as a group, unmedicated, had these problems. So it's interesting how history gets lost; it's teachers essentially who are supposed to keep all of this alive.

CS: So, if you think about all of your contributions and publications and books and journals, are there any things that particularly stand out?

RS: You.

CS: Well, thank you very much.

RS: I think I'm an educator; I have always thought of myself as a scientist educator, but really what that means is to educate about science. I've never been able to do science without colleagues, and, so, if I want to be remembered for anything, it's more for trying to inspire other people to use information properly.

- CS: Well, that would suggest to me the *Psychopharmacology Training Manual*, which the first edition was also somewhere in the '70's.
- RS: 1970, yes.
- CS: And, it's gone through a number of editions.
- RS: It's a spectacular book.
- CS: How did you come to decide to do that?
- RS: It's the same as with the Journal. There wasn't a book that I felt that we could easily use, that you could carry around. And, I saw the *Washington Manual for Internal Medicine* and contacted that same publisher, Williams and Wilkins, and said, it's time to have something like that in psychopharmacology, and they were very willing to back it.
- CS: Okay, now, I'm supposed to ask you about any honors, awards and distinctions that you received during your wonderful career?
- RS: Well, I think there's some that have stood out in an interesting way. The late Frank Ayd, who just died, was a long time friend through the ACNP, somebody whom I admired, because he also had a commitment to bring drug information to people and making sure that bad things didn't get hidden. Actually, my very first paper that I wrote for the *Journal of the American Medical Association* was on *Retrograde Ejaculation with Thioridazine*, and I had a devil of a time publishing that paper. They did not want to publish it, because it looked bad for the drug. And Frank had always been somebody who supported getting at both positive and negative drug effects and, so, my very first reward was the Taylor Manor Psychiatric Award, which pleased me a lot, because it came from somebody I had a high regard for. Then, as you know, you and I, received the Vestermark Award from the American Psychiatric Association, which is an educator's award. We also won the award for the second time for our work together on the curriculum for psychiatric residents in psychopharmacology, so I had the opportunity to share that with others. I certainly had many opportunities to be visiting professor in various places, which has taken me around the world and been a very vital part of my life and growth.
- CS: So, as you look back over your career, how would you...
- RS: You're making me feel old.
- CS: No, no, no, you're getting younger every day. You look terrific and sound terrific, but I'm supposed to ask that question. Are you happy with the way things turned out in your professional life?
- RS: Yes. I'm not necessarily happy with what's happened to my profession, but I'm happy with my professional life.
- CS: And, which profession is that, pharmacology or psychiatry?
- RS: I would say with psychiatry. I think the pendulum has now swung too far in the direction that I meet young psychiatrists who never have any time to

talk to patients. It is very disconcerting to me to see clinicians who don't know the difference between being demoralized and being depressed, who don't really recognize that some kinds of anxiety can be dealt with by reassurance. It is disconcerting to hear people now talking about intervening in prodromal schizophrenia when we don't really know that those people are going to turn out to have schizophrenia or not. Some of them may end up being bipolar. Some may be having adolescent turmoils and we don't know very much about that. So, that component of psychiatry, and I'm first and foremost a psychiatrist, that component I find very distressing. I don't know if you're on Barney Carroll's 'mailing list...

CS: Oh, yes.

RS: Then, you see about controversies, as for example that somebody's marketing a diagnostic test for genetic variance that might predispose you to bipolar disease. You know, to me, that's not where we are.

CS: So, if you look ahead to the next five years, could you comment on what you think would be the exciting developments that might actually have clinical relevance? In your own area of kinetics, we're certainly learning a lot more about how to define the genes.

RS: I think kinetics is important and I think genetics is very important. But I think what is even more important is not looking to one single avenue. I think the future lies in trying to bring things together. You have to pull them apart for a while, but if you then pull them apart and go down those separate pathways without really finding ways to bring a synthesis back together I think you forget about people. When you talk about treating gene defects, you are not talking about treating people.

CS: This brings us back to current areas of gene - environment interaction, which in some way seems to complete the circle that you started; it very much takes into account life, as well as one's genetic equipment.

RS: Some recent obesity studies looked at the fact that men are more likely to overeat, because they're sitting around with other men who are overeating, whereas women are always talking about their dieting, or when they eat together are always trying to eat less and show each other that they're eating very little. You know, it isn't simple and I will continue to do work in this area. It will try to make sure people understand that it isn't simple and to try to tease apart the elements that can be revealed.

CS: Well, I think that's a wonderful place to stop. Dick, thank you very much. I think that the ACNP is honored in having had you as President. I remember the Sullivan lecture very, very clearly. You were kind enough to ask me to participate on that program and I owe you a lot of thanks for my own career and thank you for this interview.

RS: Happy to do it.

STEPHEN M. STAHL

**Interviewed by Andrea Tone
San Juan, Puerto Rico, December 13, 2004**

AT: My name is Dr. Andrea Tone and we're at the 2004 ACNP Meeting in Puerto Rico and this afternoon I have the pleasure of interviewing Dr. Stephen Stahl.* Thank you very much for agreeing to be interviewed.

SS: My pleasure, Andrea.

AT: Let me start by asking you how you got interested in medicine.

SS: I was interested in medicine from the very beginning of school times. In fact, I have been told I drew a picture, as a kindergarten student, drawn with a stethoscope around my neck, doing rounds on patients in bed. I don't know where that came from, but I always kind of thought I'd go into medicine and I was interested in science. I did, science fair projects, which school boys do, even, in grade school and junior high. And, in fact, the ones I always chose, after about the eighth grade, were all in the brain, so I always had very much of an interest in that from a very young age.

AT: You don't know where that came from?

SS: No, I don't know. I just had an affinity for it; it captivated me and interested me, but I was never quite sure whether I wanted to be a neurosurgeon or a scientist or a neurologist or a psychiatrist. It took me a while to figure out how I wanted to skin that cat, but I was always interested in how the brain worked. I found it to be fascinating.

AT: OK, so you did pre-med studies. What was your major?

SS: I was in a kind of very interesting program, called the six year medical program, an honors program where they, actually, accepted a limited number of high school students right into medical school. And there were thirty of us that had two years of undergraduate school at the North Campus of Northwestern University in Evanston, and we were already accepted to medical school if our performance was okay. So we had an accelerated undergraduate curriculum and, then, went to medical school after two years of college.

AT: You never had any doubts along the way?

SS: No, I never looked back. I was interested in a lot of things. I marched in the marching band; I did that as well for the first two years of medical school. I, actually, went overseas with my professor before my freshman year in medical school, which would have been at the end of second year of college. He went on sabbatical and I went to Germany with him for that

* Stephen M. Stahl was born in Wauseon, Ohio in 1951.

summer, doing research, as well. So, I had already a connection with one of the medical school professors in college and was doing research at the medical school while I was, actually, in Evanston. And, I was, also, playing in the marching band in Evanston when I was in medical school in Chicago. It was a very good program, a very rich program that allowed you to work outside of curriculum and work at your own pace.

AT: Now, you seemed to have expressed, very early on, an interest in neuropharmacology. At what point, in your extended medical education did the light bulb epiphany occur and you say, “Ah, ha, this is it”?

SS: I was interested in the molecular nature of learning in a planaria and goldfish in high school. So, I think the light bulb was a little dim then but going on and I was, actually, always interested in how drugs worked in the brain and didn’t know whether I should be a neurologist or a psychiatrist. I was, also, kind of distracted by the glamour of neurosurgery, but, actually, found that the reality is that most neurosurgeons didn’t help that many people and the techniques were very fascinating, but the outcomes weren’t so good. So, I didn’t really decide that I was going to be a pharmacologist of the brain until I was, maybe, a junior in medical school. At that point, I was in a MD, PhD program, trying to decide whether I was going to do biochemistry or pharmacology, whether I was going to be a neurosurgeon or neurologist. And, actually, I decided to be a neurologist and got my MD and a PhD and saw myself as a pharmacologist of the brain. I thought that psychiatrists were a little loony, maybe, and a little bit difficult, and I wanted to be a real doctor, so I aimed first to be a neurologist.

AT: Can I pre-screen that? What was happening in psychiatry at this moment? Take us back to that time and let us assess psychiatry through your eyes.

SS: Well, now, you’re looking at a nineteen or twenty year old, who grew up in the Midwest, and whose parents wanted him to be a doctor, and were worried about why he’d want to go to Chicago instead of Ohio State and being a real doctor was not what a psychiatrist was in their minds. And, so, I think I grew up with the idea in that era, which would have been in the early 1970s, that psychiatry was not too rigorous or quantitative; it wasn’t a real science; it wasn’t a real specialty. I had a Midwestern work ethic where people were the salt of the earth. If you whined and engaged in bi-coastal “psycho-babbling” you had a “mental” illness, but real patients bled to death and had heart attacks. And, I was supposed to take care of real patients and, in fact, for a long time I did a lot moonlighting in the emergency room, which I enjoyed immensely. I was conflicted about going into psychiatry, because I wanted to be a real doctor and, I didn’t think psychiatry was real medicine. So, I, actually, went into

internal medicine after I did my PhD and then into neurology. And, to my dismay, I found out that there was very little medication treatment of neurological illnesses in the seventies and the best medications available to treat brain disorders were, actually, in psychiatry and they actually, worked. Most neurologic illnesses didn't have treatments and the treatments were not very good, although, there were some in epilepsy and in movement disorders, the areas which I was really interested in. I also found that for the vast number of people, who suffered from psychiatric disorders there were treatments available. And there was the promise of neuropharmacology, which, actually, came to be realized in many ways in the late part of the twentieth century. I could foresee that there will be, perhaps, a richer environment in psychiatry than in neurology. Also, neurology departments are small and neurology, as a clinical speciality, can be difficult. It's hard to be a good clinician and to make a living in academic neurology. There wasn't the chance to have as much freedom to do research and, the possibility to, actually, just have a research career was, perhaps, greater in richer, psychiatry departments, which were larger, had more resources. Psychiatry was a much more exciting field to be in, in the early seventies.

AT: Now, already, biological psychiatry had taken off; did you find, in Chicago, the last remnants of the psychoanalytic tradition?

SS: Oh, there were more than the last remnants of it. There were, actually, turf wars. There were ideas that you could, either be psychodynamic or biological, but not both. There were schools of thought that you kind of had to decide. And, I kind of decided to be so biological that I didn't even become a psychiatrist at first. I went into neurology and, then, I said, this is not for me. I was at UCSF in neurology, because I did not want to be psychoanalytical at all.

AT: How come?

SS: Because I thought it wasn't scientific; because I thought it was an affectation; it was not rigorous and not useful, and I didn't understand it. Then, I can remember coming to my first few weeks of psychiatry residency, seeing David Spiegel, who's a well known psychiatrist at Stanford doing hypnosis, hypnotizing a patient, which I thought was all baloney, until I saw it happen for real, and it just shocked me. I mean, I actually, discovered there was an unconscious and I had thought there was no such thing before. I was blown away by the unconscious and the fact that there was a dimension of that. Luckily enough, I decided to go to Stanford, which kind of had both warring camps, not reconciled but coexisting not always peacefully. So, going through a residency was very, if you will say split brain or two existences; you had this highly biological, catecholamines,

neurotransmission side and, then, there was this extremely psychodynamic, psychoanalytical other side where you had supervision by psychoanalysts and most of us were encouraged to go into analysis. I, actually, went into therapy. I went that far. I didn't do analysis. Somebody did a calculation once and said that the cost of the analysis was about one Porsche over the course of a residency and it might be smarter to buy a Porsche than to have analysis. I neither had an analysis nor a Porsche, but I did decide to believe in getting my own therapy and doing therapy. It was a very difficult thing, because as I said, you had these warring camps that hated each other, even within the same department, let alone the same field and there was nothing that they had to do with each other. And, trying to reconcile that was my job; the idea that you do therapy and give medicines to a patient was kind of radical, at that point. And, I gather at different places the two approaches were reconciled perhaps, better than at Stanford. In the early seventies, there were places like Washington University that was so hyperbiological that there was no psychotherapy. Then, there were a lot of places in New York, like say, Cornell Westchester programs that were so analytic that they didn't know there was a brain. So, I think I was quite lucky; although, I didn't quite understand how to put those two warring camps together I was exposed enough to them sufficiently that, to this day, I do some therapy. I understand the cognitive parts of therapy, perhaps, better than the analytic and certainly believe in education and destigmatization. I refer patients to therapy and I think it's a powerful tool.

AT: Why did you decide to leave UCSF, where you did your residency in neurology, to go to Stanford?

SS: I really didn't feel that I was cut out to be a neurologist. I was aware of the difficulties of having a career in neurology. They have to do a lot of clinical work to make a living, and the illnesses seemed to not be amenable to drug treatment as much, at least in the short run of the next few decades. And, also, what I'd done as a PhD was to work on neurotransmission and drugs that modified neurotransmission and these were largely not used in neurology, with the possible exception of movement disorders. So, I felt that it would be best to be associated with a state oriented program. There were several in the country at that time. Yale was one of them; Stanford was another. I decided to go to Stanford to become a psychiatrist, despite myself. I probably had matured a little bit; I had spent many years working in the emergency room and felt like that I, actually, could, leave being a "real" doctor and become a psychiatrist. I didn't feel at that time that a psychiatrist was a real doctor. What I thought of myself, basically, was a pharmacologist of the brain. Actually, I haven't completely left

neurology, because as my career has gone on, I have worked quite extensively in movement disorders and have had some interests in dementia. I don't feel uncomfortable in moving across the neuropharmacology spectrum working with those disorders if there are opportunities to do research there.

AT: Tell us who your mentors were at this time?

SS: My first mentor was E. A. Zeller. Zeller was a Swiss biochemist, who had a position in the Swiss Army during World War II and, afterwards, came over to the Mayo Clinic and, then, to Northwestern. I believe, in the late fifties or late forties, he, actually, was involved with the discovery of monoamine oxidase and discovered the first MAO inhibitor, iproniazide, which was an antituberculosis drug at that time. So, he was a prominent MAO enzymologist and we worked together on neuropharmacology when I was a freshman and sophomore in college. When I started at Northwestern as an undergraduate, I was commuting down to the medical school and worked there in the summers. It was with Zeller that I went on sabbatical to the Universitat Konstanz on the Bodensee in Germany. We worked on flavin biochemistry, because MAO is a flavin enzyme and found that some of the MAO inhibitors are bound to the flavin part of the enzyme. But, he was at the end of his career and I decided to move to the University of Chicago, so my MD is from Northwestern and my PhD from the University of Chicago. At the University of Chicago I picked up two important mentors, one of which was my PhD supervisor, Herb Meltzer. And Herb and I started a long collaboration, which lasts even till today, and that would have been in the seventies. I got my PhD with Herb and, also, during that period of time, I was sort of adopted by Danny Freedman, who's a distinguished past leader of the ACNP and other organizations. I left Chicago to go to San Francisco to do neurology and he never quite figured that out why I did that. But, I came back to the field and worked with the people at Stanford, Jack Barchas and Roland Ciaranello. Then, I moved on from Stanford training, and joined the Stanford faculty.

AT: Your career path has been remarkable in many ways, including the fact that you were able to get an MD and a PhD in an astonishingly short period of time. You also have a vita that weighs about three tons. What drives you and what were the research interests that you had early?

SS: I was interested in treatment of mental and neurological illness with drugs, and my first job, outside of my residency, was to be the medical director of a schizophrenia biological research center at the Veterans Hospital at Stanford. I was, also, an assistant director of, what was known in those days, a mental health clinical research center. These were the early days of rating scales and of doing biological tests on blood and urine and CSF,

and I had a small laboratory doing some of those things. I was very interested, really not so much as what was wrong in mental illness, but how to treat it. Certainly, those things go hand in glove. I was always really interested in being a psychopharmacologist. I was interested in testing new drugs and trying to understand how drugs that we already knew worked and, also, working with new drugs that were coming forth from the pharmaceutical industry. At a fairly young age, I was approached to consult for one of the drug companies that was building a brain research institute just outside of London, and they asked me for advice on setting up a normal volunteers unit. In those days, it was easier to do normal volunteer work in the UK than in most other countries; regulations and approval of medicines were, in Europe and the UK, ahead of the United States. They tended to approve many drugs up to ten years faster than in the US in the 1970s, and, for various reasons Merck, decided to build a brain research institute there. I went over to join that group and run a normal volunteers unit. I also had a small basic science discovery laboratory and, eventually, was given responsibility to do Phase II studies in Parkinson's disease. I was in the UK for about four years, and while there, I worked also at the Institute of Psychiatry in London. During that time, I learned quite a bit about drug development and how it was done. This included the science, as well as the regulatory realities and some of the financial realities of doing research on drugs in human. It also involved bringing drugs out of animals and crossing into man, doing early clinical studies and, of course, late clinical studies for registration. It was quite exciting. I thought I was going to have a career in industry, perhaps, but it happened that that group really did not have a lot of success and did not have a lot of support at the higher corporate level to licensing new drugs. So, the drugs, that were invented, didn't get high priority on safety testing. As it turns out, that group really hasn't had any success in the CNS in thirty years. I could foresee that was going to happen, so, I went back to academia, after having a very good time in industry and used my experience with Merck as a way to kind have a background in industry. Then, I moved to the other side of the table again, to the academic side. I went to UCSD, where I've been in one position or another, till today. I came back to be Chief of the Psychiatry at the VA and a professor, full time, at the University at UCSD. And, I did, again, some basic science work and some more scholarly work in a mental health clinical research center and, then I did more and more clinical trials over time.

AT: How important has it been to you to continue to have patients? There are a lot of people at ACNP, who really have given that up.

- SS: It is something that I think about every few months, because of the pressure of time and the travel, but in my own personal situation, I can't do that. I'm doing a lot of teaching and writing now and a lot of the people, who hear my lectures or read what I write, are clinicians. And, I believe, you lose your touch with reality if you stop seeing patients. In fact, I think, if you're not a person that would be generally felt by a community of your peers to be someone they'd send their mother or their wife to, I don't think you can speak with the same credibility. So, I have never stopped seeing patients. In fact, when I was in the UK, I, actually, got a medical license. It sounds like some sort of a disease; they called me a VOD, a visiting overseas doctor, but I got an actual medical license and saw patients, even the four years that I was in England, so all the way through my career I've always seen patients to this day. I only see them one day a week now, but I see three new patients a week; they tend to be very, very sick and difficult. They are usually sent by other doctors. The rest of that day, I see follow ups that come back. I think that's very important for not losing the clinician's perspective. It's very easy to be real smart treating somebody else's problems. What happens when we see patients is that you make mistakes and you learn from them, and it's a humbling experience. I've often said that the most important visit that a clinician does with a patient is the second or third one, not the first. Lots of people can come up with an elegant, scholarly, very clever plan for what you should do, based upon what's happened in the past, but if it does not work, it is on the second visit when the patient comes back that they're staring you in the face: "Now, Hotshot, what're you going to do next"? And, it's really that first and second adjustment of your mistake or your misstep that really separates the really good clinician from the kind of theoretician the person, who is pontificating, but is not really accountable for his errors. I think, that to be able to manage your clinical errors, to live through them, is what makes you a good doctor or not. All of us make errors and you can forget that if you're never accountable for your own errors. If you don't see patients any more, it's very easy to think you're very clever. You get humbled very quickly when you see patients in an afternoon and realize that not everything you thought might work. Adjusting to that is what makes, I think, you a good clinician; and, then, it really makes you feel great when things work.
- AT: That's true. It must be easier to alleviate human suffering on paper than in practice.
- SS: Yes.
- AT: Do you get patients, who suffer from a particular disorder, being referred to you, or do you see patients suffering from a range of mental health disorders?

SS: I am pretty much a generalist. I think one of the problems is that, since I don't see them in the hospital, they can only have a certain level of acuity, so, obviously, people who are acutely psychotic or acutely manic, wouldn't come in the office, at least not very often. Sometimes they, actually, do, because they get unstable between times they have their appointment. And, I not only see adults, men and women, but when they come I also see children; I see elderly; I see adolescents. Affective and anxiety disorders are a large part of my practice, but there's a great deal of bipolar disorder that I'm seeing now more than ever, and psychosis in younger patients. So, really, it's across the whole gamut. I find it very interesting. I won't say no to anybody.. It's a pretty general psychiatric practice.

AT: Looking at your research record, you've published on so many different things: on hormones as antidepressants, on schizophrenia, on sexuality. I know your work on anxiety best. Looking back, do you see yourself as going through different phases in your work: at first you were interested in X, which led to Y, and so on, or are you more of a renaissance man, a doctor, a scholar, interested in all?

SS: I know a little bit about everything and nothing about anything.

AT: I don't believe that.

SS: That's what it amounts to. I, actually, started out more in schizophrenia and have spent a lot of time in depression. Those two areas would be, probably, where I started. When I first started my career, I had fantasies of really understanding and making some big breakthrough in how the brain worked. Then, I began to do more clinical research and translational research, kind of straddling clinical and brain research. And, after awhile, I decided that I would work on new drugs for new diseases, because you can really improve the outcomes of people if you made better drugs. And did that for a long time and had fun with that; I enjoyed it. And I did clinical trials across the gamut. Then, I began to see myself as a very tiny cog in a very big machine who does not even write the protocols of studies, because often the companies do that. Then I realized how much good one could do by just taking the drugs that were already on the market and taught people how to use them closer to the ideal. When you look at the level of actual practical use of drugs compared to best practices there's a huge gap. I first became aware of that when I wrote my textbook. When I completed it, the response in the field was astounding to me. It changed the course of my career because there was such intense interest in courses based on the book. The book is a general use of pictures to tell a story, as well as simple words to translate complicated concepts. This is when I became more and more of a generalist because

writing the book forced me to learn all the sub-areas of the field, many of which I kind of knew, only fairly superficially. In doing that, it woke me up to the need for good teaching. There's this unfortunate truism that you're paid to do research and you're promoted for doing research but you only bootleg the teaching. The saying is that the glamour is in research, and the people, who are not good researchers see patients and the losers teach. And, the result, of course, is that for teaching, the resources are not there, the glamour is not there and a lot of the time the teaching is not done well. There is a big hunger for good teaching. There is actually a science to teaching, much of which is done poorly in medicine. Often in medicine content is king, and the prince is the teacher and the last person you want to care about is a student, because they're not important in the hierarchy. But, adults don't learn optimally when the content is king. Adults learn when information is presented in a participant focused way and, so, trying to make materials easy for the participant, even if it's difficult for the teacher and even if you have to leave some of the content out are, actually, some of the best ways to teach adults.

AT: When we assess your career, which is clearly only at its' mid-point, what do you think your key contributions have been to the field of neuropsychopharmacology?

SS: Well, I don't know, I think that's for others to say. I'm not sure I've made very many. I think that if there's any, I've tried to communicate to the practitioners to help them become better doctors and prescribers and diagnosticians. It's been interesting to be a small piece of the machinery that invents new drugs. In many of the psychiatric drugs that are on the market today, I've had a role as being an investigator and that's been fun. But, I think lots of people contribute to that. I don't think I, necessarily, did that in any unique way. I think what is interesting is how you define your constituencies. I probably have more influence among the prescribers than I do among opinion leaders. There's a group of elite people, say, 500 people in the ACNP or the 2,000 to 3,000 people, who have investigator grants, RO-1's, and there are 40,000 psychiatrists in the US. And half of the 150,000 primary care physicians prescribe, actually, more psychotropic drugs than psychiatrists do. And, you double that number, worldwide, and, then, you also have the nurse practitioners, who prescribe. My constituency now is really the people who want to know how these drugs work and how the diseases can be understood and how to, practically use drugs often with combinations for patients that are hard to manage, that don't respond to one drug. So, I reach now, with my textbooks to 50,000 to 100,000 people in each edition, and with the courses to 250 people per week-end in twelve week-ends a year, that's 3,000

people a year. We also send out CD-ROM's and so forth, fifty thousand at a crack. So, my group has sent out a couple of millions CD-ROM's, so far. And, we write articles in various psychiatry journals each month and that hit 40,000 people a month. Many of those are not elite but some of those are rank and file; they are very often good doctors and prescribers who care very much about their patients even if they're not the beautiful people of the academic realm. Some of them are clinical investigators. Perhaps forty percent of my efforts are outside the United States these days, perhaps as a result of my textbook. When you use iconography to tell a story about mechanism of action, how the brain works, it communicates the same message to people who don't speak English. And, it's very easy to understand, because it uses a universal language. So, the thirst, in some ways, for this information has been even greater outside the United States than it is in the United States, because it doesn't require words in English. And, now that we've gotten into animations and showing relationships in space and time it is becoming even more interesting to people who want to know psychopharmacology. So, if I've made a contribution, it might be in the area of communicating simplified concepts of some of the rules of psychopharmacology, for which there are many exceptions. I talk mainly about the simplified rules of how the brain works and how the medications work and how to use them.

AT: Right. I recall attending the lecture you gave in Nashville last summer, where you talked about how benzodiazepines have never really gone out of fashion, and explaining it made sense to me. I wonder if you had any scientific or, perhaps, philosophical misgivings about that internists, family practitioners are the primary prescribers of psychotropic drugs. Do you think they understand, psychopharmacology enough?

SS: Some do; some don't. I've always said that eighty percent of doctors are not safe when they are prescribing. Twenty percent are safe. Three percent are excellent. And, I think that goes for all the specialties and psychiatry is not any better than any other specialty. Of the 40,000 psychiatrists in the USA, about 6,000 prescribe eighty percent of the antidepressants and another 5,500, not necessarily the same doctors prescribe most of the antipsychotics. But, from our courses, many of the attendees are not psychiatrists; they are what we call, PCP's, primary care physicians. At UCSD, where I am, we have joint program where you can get both family practice and psychiatry boards. These primary care physicians are those who are not interested in short appointments and running people out the door very quickly, but interested in listening and taking care of patients' behavioral complaints. They tend to have longer appointments and they tend to prescribe more psychotropics. They go to CME courses that are

designed for psychiatrists, and some of these practitioners are excellent. I think when you are cavalier about these drugs and give them out like candy, no matter whether you are psychiatrist or a PCP it's not a good idea. I think if you have children who are depressed and you give them a sample pack and say come back in thirty days, and call me if there is a problem, without explaining anything more, that can create some problems with the failure to observe the activation of side effects and, possibly, suicidality caused by some of the drugs. In fact, we are experiencing a major backlash against that now. Being sloppy and cavalier is bad, no matter what your specialty group is. So, actually, I'm kind of a little bit of a maverick on this. There is a kind of a guild mentality and an elitism that you must be a board certified psychiatrist and that prescribing should be relegated to the elite, and certainly not to psychologists, who are desperately trying to get to prescribe these drugs. I don't define my constituency or the people that I'm interested in writing for or speaking to as psychiatrists, even though about seventy percent of them are. It includes primary care physicians, physicians with another specialty background, nurse practitioner, or pharmacists in some states or in some systems like the VA that allows pharmacists that they can understand how the brain works and how to become more competent as a practicing psychopharmacologist. When you start looking at other parts of the world where there are so few psychiatrists that you have to leverage those psychiatrists with different types of practitioners in order to get the healthcare delivered, you see the need for the kind of work I'm doing. Even when I am in Ohio that I'm from, there are no psychiatrists in the small towns, and, to get a psychiatrist, you'd have to travel fifty miles and there are only a few. So, in the middle parts of the country of lower density there are not a lot of psychiatrists. We certainly need to train to prescribe psychotropic drugs other than psychiatrists. I always try to encourage adult psychiatrists to practice adolescent and child psychiatry to the extent that they can become competent. There's a vast under availability of child psychiatrists and, sometimes, pediatricians treat child psychiatry cases, and, sometimes, general psychiatrists do. Certainly, the best thing would be to train more child psychiatrists, but since that isn't happening and I'm not sure it will happen soon, I think using every interested and capable professional, who can be made competent by good training programs help solve the problem of lack of child psychiatrists.

AT: What do you think, why becoming a child psychiatrist is less appealing?

SS: First of all, it's a little bit longer training. Second of all, it is sometimes not as well compensated. Another problem is that too much of the time child psychiatrists are not spending time with patients, but managing others.

If you are a child psychiatrist you are rapidly put into administrative jobs and people in administrative jobs are paid better and have more regular hours. Also, there seem to be a lot of academic openings in child psychiatry, but not necessarily, a lot of research openings, because there's such a need for services. I think it's a very interesting field, but, the problem is, that there's very little evidence based medicine in child psychiatry. You think it's bad in adult psychiatry where we are using drugs empirically and throwing them around at people, based on history and anecdote and somebody's last good idea, it's even worse in child psychiatry. And, now, I don't know that there will be studies done because the drug companies have been punished severely for studies that they did in children; and the drugs studied seemed to be toxic. I think that's an overgeneralization but there is little incentive left for anyone to study children again. And, I think that situation is not going to be remedied soon and, so, we will be doing a lot of treatment in child psychiatry with drugs and combinations for which there's not really been evidence that they work, even though, they probably do work. The guidelines to treat in child psychiatry are not as well developed as they should be and, so the real advances in the field are really coming in the child applications from adult psychopharmacology.

AT: How destigmatized has taking psychopharmaceuticals become? I once had a fear of flying and I took Ativan (lorazepam) to allow me to board a plane. It was, for a time, what got me to board a plane. My doctor thought that this would provide exposure therapy and after flying enough times without incident, there would be no need to take the drug. She was right. But, I couldn't write about this experience until I had stopped taking the medication. How has this kind of stigmatization changed over time? Have we gotten better? Where are things now?

SS: Getting better but still problems. I think the word, schizophrenia, is still pretty frightening to people. I think women still don't like to be seen with Xanax (alprazolam), in their open purse as people walk by and look at it by accident or men don't want to, necessarily, be seen as "wimps" that take medication. Men are still supposed to sort of suck it up and overcome adversity. And, there's still an idea that there's a character defect and that they're not trying hard enough to overcome their symptoms if they are taking drugs. And, there is also an increasing worry about cosmetic psychopharmacology. For example, if you have insomnia, people say you should just not work so hard. There's no such thing as a sleep disorder. If you can't stay awake, because you have narcolepsy or sleep apnea, they say you're just supposed to "knock it off" and not take a wakefulness drug. If you have depression, you are supposed to "get over it". And, at the milder end of the spectrum, it's still thought that,

it's your choice and that you're not trying hard enough to become better. People still think it's like plastic surgery, of erasing your face wrinkles or enhancing your breasts or something. And, so, there's still a lot of stigma and misinformation about psychiatric drugs. I think that the fact that this topic is still written about, even today, suggests that we still has stigma attached. But it certainly it is much better than it was. We certainly would have never seen commercials and the ads in the past that we now see, and certainly would have never seen celebrities talk about their disorders, if it would not be better. And it happen that I sit on an airplane and people seeing a journal that I'm looking at, figure it out that I must be a psychiatrist, and tell me about the drugs they're taking.

AT: Sounds like me.

SS: Well, it has changed, but I think it has not changed sufficiently, and I think there are still, barriers to receiving treatment. I think so that we're on the right track, but we still have more work to do.

AT: Do you think that cynicism about the pharmaceutical industry and its myriad products runs the risk of restigmatizing?

SS: Absolutely. I think the pharmaceutical industry has always been sort of suspected of inventing psychiatric illnesses. In other words, the diagnosis was Xanax and the treatment was panic disorder and there was no such thing as panic disorder before Xanax, or .whatever gets better when you give Xanax, is a Xanax responsive syndrome. Many people still think that each company invents its' own illness, gets rich from it, by giving people that have marginally or even fake symptoms drugs that they don't need for symptoms they don't have. The theme out there is that the symptoms are all in the head, and drug companies get rich by ripping off patients. It's, of course, a gross overstatement. But I think if trust in the pharmaceutical industry does not improve, if they don't earn it back, and the experts that are the face of the pharmaceutical industry are seen as being in the pockets of the companies saying what they say to make money, rather than because it's the truth, if that doesn't change, then, I think it will set us back into stigma, because people will say, there's another illness that's invented. For example, there's Bipolar Spectrum Disorder, Bipolar I and Bipolar II Disorders, and there may be other types of Bipolar Disorders, and a lot of people are cynical saying, everybody's bipolar so that the pharmaceutical industry can give a lot of unnecessary drugs to a lot of people, who, really, just have interesting personalities and nothing wrong with them, that's a huge risk, right now, that we run. I think that it's urgent that we earn back our credibility, so that when there's an innovation, it's believed instead of being considered a marketing hype.

AT: Do you think that we, as a society, tend to exaggerate or overreact to the dangers of drugs?

SS: We certainly are now. I think that there's a risk benefit ratio that is not well understood by the average consumer. Maybe, it's the pharmaceutical industry and its' experts that are creating the problem by using kind of terms, as for example magic potion, miracle drug, cure, which are really much more oversimplified than reality, instead of saying that .drugs are all poisons at some level, they may hurt few people, but if they wouldn't help a lot of people they wouldn't be on the market. And, there's, also, this idea that if you have millions and millions of people taking the drug, you can't understand the risks that might occur in a million people until you've studied a million people. So, if you study it in two or three thousand people, that is about the limit to what is economically feasible, you understand what proportion of people per thousand have a side effect, but if the side effect occurs in 1 in 10,000 you might, won't even see it yet. So, there are some side effects that are only going to be discovered once a drug is on the market. And, right now, there's a worry that the FDA can't be trusted any more than the drug companies, and the experts, that we need a new FDA. We need a second branch, because the group that approves drugs can't be trusted to take drugs off the market that they've approved, because that will be embarrassing to them. That's the way some of the arguments go. I think that the reality is that certain drugs that go on the market need to be monitored and that it may be still worth to keep drugs on the market that cause rare side effects. That drugs sometimes need to be withdrawn doesn't mean that the drug companies were hiding side effects, or that the FDA and the doctors did not do their job. You know, one of the things that happen with these safety issues is that they don't occur like snapping fingers.. They kind of dawn on you and when you're working for a company and there's billions of dollars at stake, it's true, you don't want to see the exposure of some information before it examined whether the drug is toxic or not toxic and what are the things that go for it and against it. So, if the public wants new innovations, they need to, at least, have a pharmaceutical industry that can make a profit or else that whole industry goes away. We could debate how much profit, but if you kill the whole industry there will be no new drugs.

AT: Let me pick your brain very briefly, because I know you have to go. On the history of benzodiazepines, you were in med school right around the time when so many media reports came out about the hazards of benzo addiction. If you look at usage rates in the United States and the UK, things started to dip in the late 1970's, but elsewhere consumption went

up and it remained really very high relative to what it is in the United States.. How do you explain that?

SS: I think that a lot of this is societal perception and not psychopharmacology. I think that when you went from barbiturates that caused seizures when you withdrew from them and deaths from overdose, if you even took a handful of them, to drugs that, apparently, relative to barbiturates, had no dependence and no overdose potential, it appeared that they didn't have any. So, the pendulum swung away the other way. You were excited because it seemed that these new drugs can be used with impunity. It was a storybook existence that was overstated and oversimplified. And, because, relative to what they replaced, they were a heck of a lot better, it took a long time to recognize that there were withdrawal problems and that were people, who were dependent on them and abused them, particularly, when they abused other things. And, even today, as in France and Italy, there are many countries where they are used more than in the USA. In some countries today, there isn't the social stigma to take a benzodiazepine or to prescribing them. In this country, there is kind of a bifurcated group of physicians and patients, some of whom will come into your office and say, "I'm not going to take this, no matter what", because they think it's kind of a heroin and, then, there are other people who think it's OK to take them. If a person says, there's no way I'm going to take benzodiazepines, it's just easier and faster to say, alright, even if they need one. There's no question that benzodiazepines work. The question is risk benefit ratio. You have to look at risks; you have to look at benefits; you have to weigh them; you have to think; you have to calculate.

AT: What do you think about the repositioning of SSRI's as anxiolytics?

SS: They are probably excellent first line treatment and I would agree with the repositioning treatments for most anxiety disorders with SSRIs. However, they work late; they have early side effects and, often, they cause only fifty or sixty percent reduction of symptoms. And, if you're not responding, or partially responding only you can earn your right to have a top up of benzodiazepine until they have no symptoms. It's not good for people to suffer, and it is not just merciful to reduce symptoms, but also because there's a kind of diabolical learning that the brain has. The brain learns to have its' symptoms. It seems to be the case, maybe even, in schizophrenia, but, certainly, in pain and anxiety disorders. Anxiety begets which begets treatment resistance. In fact, the brain may, actually, shrink. And, perhaps, shrinking the size of your hippocampus and causing diminished neurogenesis or, at least, synaptogenesis, is not good for the brain. So, this leads many of us in practice to be worried about symptoms, not just

because they bother people, but because the brain may be changing. So, the idea is to suppress all symptoms that the brain stops its' diabolical learning, stops its' atrophy, and let it have a chance to recover. And, then, pull off medicines one at a time, and if with slow dose reduction the symptoms don't reemerge, then, maybe, your brain's healed, if that's the word. I think that we are in an era, right now, where the careful good clinician is saying, you don't get any points for suffering; just because you can tolerate these symptoms, you get no points. The issue is that a lot of patients think they get points if they can stop their medicines and stand the residual symptoms or take fewer medicines; they think that they get more points in heaven or some place, the fewer pills they take. Not so. You want to fight a fire with a squirt gun and wait and see if flames go down, or do you want to douse it, get it out, make sure that the coals are cool and, then, you move on. So, it's a little bit like the brain's burning and those circuits are firing and they're angry and they're active and shutting them down with symptomatic treatments, no matter what they are, it doesn't matter. Pregabalin is a new drug; Gabapentin, Gabitril, is a new drug that can stop symptoms of anxiety. So, there are ways to, perhaps, not use benzodiazepine and not use SSRI or SNRI. There are other possible ways to do it. It doesn't matter how you do it, I don't think. It just matters that you do it. You find a tolerable way to suppress symptoms, then, you back off the number of treatments, and the doses, and see if you can get lucky but often you can't because the patient needs life long treatment. So, I think that's where we are today in trying to reduce symptoms. In fact, I have written, a couple of articles on that. I wrote one called *Do Prophylactic Antipsychotics Keep You From Catching Schizophrenia?*

AT: You do have wonderful titles.

SS: There's another one I wrote which is, *If You Prepay For Pain, Does It Cost Less*, because it looks like if you get treated, actually, with pain medicine before surgery you need less pain medication afterwards. And, then, finally, I wrote one, *Can Psychopharmacology Inoculate You Against PTSD*, because it does look as if, maybe, twenty-five percent of subjects after an overwhelming stress sort of get PTSD and seventy-five percent won't. The symptoms in people who get it, are reduced by giving a β -blocker right after the stressor and, maybe, because when you have epinephrine raised during a terrible stressor, that sensitizes the circuit that gives more emotional meaning to it, and if you block that with a beta blocker, you prevent the over-learned association so that any other stimulus, that reminds you of the original, doesn't trigger that memory again. So, it could prevent PTSD. That's a theory, but the point would be that the brain seems to have this kind of perverse way of molecular mischief,

where it does things almost against what would make any sense and, by doing that, you get illnesses and by interrupting them you stop illnesses. So, that's why clinicians would try to reduce anxiety symptoms by hook or by crook; take them all away; keep them away for a couple of years and, then, hopefully, you can help the brain decide that it isn't going to be doing those types of molecular mischief, and the incentive to do that's over and you withdraw the medicine.

AT: We have some really wonderful quips from you: bicoastal psychobabble, diabolic learning, molecular mischief. One final question: Psychopharmacology, say, twenty years from now, fifty years from now, where do you think it'll be? What you like to see it accomplish?

SS: I think, probably, within twenty years, you're going to go into a psychiatrist's office and get a buccal swab that's going to be very much like you get now going into a jail. Your DNA will be rolled off onto a slide and it'll go into a bank and you'll find out what kind of COMT genotype you have, and what kind of 5HT transporter. You will probably also find out about sixty or eighty of your different genes, all of which are risk factors that would help tell whether you would get agranulocytosis from clozapine, and one or another side effect from one or another other drug. I think you will also go into a fMRI scanner, and have it activated. You'll have a psychiatric tolerance test, I call it a psychiatric treadmill, where you, instead of being on a treadmill for your heart, your brain will be taxed by showing you a scary face to see how much is your amygdala activated, by showing you something neutral to see whether it's inappropriately activated when it shouldn't be activated, by giving you the number backward test to see what does it do to the activity of your dorsal lateral prefrontal cortex, by giving you a cognitive load test to see whether you have attention deficit disorder, problems of concentration and depression, or cognitive symptoms of schizophrenia. I think that functional magnetic resonance imaging or some sort of neuroimaging and some sort of genotyping will be in clinical practice in that time frame. I think that we are still going to have to use multiple mechanisms of action, simultaneously, and polypharmacy or two drugs together, will probably still be the name of the game in treatment. By the time you get schizophrenia, you are pretty sick, and by the time you get Alzheimer's disease, a lot of your brain's gone. By the time they come to me today, the brains of most of my patients are changed, if you will. The time to treat her was when she was a nineteen year old girl, who had her first episode of major depression as a junior in high school or as a senior in college or something like that; or to treat him when he was just a little odd to prevent him becoming schizophrenic. I think we're going to be able to prevent mental illness, probably, better

than we're going to be able to treat end stage brain disease in which the brain is already kind of decayed or has the consequences of long-term devastation, because I don't know whether we will be able to put stem cells in the brain and make neurons grow, that well. I still foresee people listening and giving information, education, destigmatization. I think that the art of psychopharmacology will still be there, trying to add the right combination of drugs and therapy for a patient. But I think we'll probably have better tools; you know, most of our tools today work on four or five neurotransmitters and there's, maybe, a couple of hundred neurotransmitters in the brain. So, maybe, for a few dozen of them we will have drugs in the next fifty years.

AT: Thank you so much.

SS: Sure, my pleasure.

GARY D. TOLLEFSON

Interviewed by Joel Braslow:
Waikoloa, Hawaii, December 11, 2005

JB: This is an interview with Gary Tollefson.* We are at the annual meeting of the American College of Neuropsychopharmacology. It is December 2005. I'm Joel Braslow.

GT: I'm actually self-employed in a couple of different jobs. I have a faculty appointment at Indiana University. I'm doing consulting, primarily, with small and mid-size pharmaceutical companies in product development strategy, as an independent corporation called Consilium, and last, but not least, I am the CEO and President of a biotech start up, called Orexigen, which is looking at neural mechanisms in the treatment of obesity.

JB: OK. Where were you born?

GT: I was born in Minnesota, a small town called Faribault, which is about sixty miles south of Minneapolis St. Paul.

JB: And, tell me about your family.

GT: It was very small. I was adopted. I have no siblings. I had a mother and father. My father died when I was twelve, so the teenage years were challenging for my mother and I, with a low socioeconomic background. So, a lot of, I'd say, self determination, self reliance is necessary to get through school, but I have no regrets, looking back.

JB: What did your parents do?

GT: They both were European immigrants, minimally educated. My father worked in electronic machinery as a technician and my mother was a cook, a chef.

JB: Where were they from?

GT: Mother from Germany; father from Norway.

JB: And, they came here?

GT: Well, actually, they were second generation; their parents came early in the last century.

JB: Did they have expectations for you?

JB: I think they did. They, of course, did not have secondary school education and, certainly did not have a college education, so I think one aspiration was to see me try to be successful and pursue my educational interests. And, of course, my father did not get to see that come to fruition, but it was quite important for my mother to see me be successful. And she took great pride in my completing college and, particularly, going

* Gary D. Tollefson was born in Faribault, Minnesota in 1951. Tollefson died in 2009.

on into medical school and residency. That was quite unique for the family to have someone do that, so it was quite special to her.

JB: What was high school like for you?

GT: Well, I wasn't a social extrovert. I was very much into sports. I enjoyed sports and that was sort of my competitor outlet. I did well in school. I was a fairly serious student regarding my academics and, somewhat socially deprived when it came to my dating scene. I didn't do a lot of dating until I went off to college. I had some good friends but interacted only with a limited subgroup of people. So, it was about working part-time, school; sports and that pretty well filled up the twenty-four hour cycle.

JB: Did you know what you wanted to do with your career, your working career?

GT: I did, in a sense. My father had a prolonged bout with cancer and spent a lot of time in the VA system. I was in a hospital environment at an early age, and obviously, it imprinted in me, fortunately, in a positive way, by a lot of the health care providers. So, I was very interested in health care. And, I think by the time I got into latter part of high school, I was also interested in human behavior and psychology. The issue was trying to wed those two things and, not surprisingly, eventually, although it was by a curious route, it led to an interest in psychiatry.

JB: Did you have mentors or teachers at that time who were instrumental?

GT: No. In retrospect, that's something, I feel a gap or deficiency. It would have been nice, but I didn't. To some degree, one has to be assertive and seek those things out. You know, you can't sit back and wait for someone to come and volunteer. I had to be very self reliant and do a lot on my own. I guess no one ever really stepped in to take that father figure role, by any means. So, it's been more through developing relationships and friendships with people and really learning, maybe, the hard way.

JB: How did you decide on a college?

GT: Well, you know, I grew up in Minnesota, so, from an economic viewpoint, the incentives were to stay in the state and to go to a state university. I had thought about leaving, but my mother was the only one at home, and to move too far away from home would probably have not been healthy for her. And I had also some good friends from high school that were going to the University of Minnesota; anyway, and I had good feelings about the university program. I knew they had a very good medical school and, so, this was a logical choice.

JB: At that time you were ready to go, you knew that you'd be in medical school in a few years?

GT: Yes.

JB: What did you major in college?

GT: My undergraduate major was in Psychology. It was a little different in the school of Liberal Arts. It was really a double major in the sense that they had a science program that was called Pre-Med, and I was, obviously, taking that curriculum. But, in parallel, the University of Minnesota was blessed with a very strong psychology program and a good legacy all the way back to Skinner. And, so, I did that double major as an undergrad.

JB: So, you thought for sometimes that you would be a psychiatrist?

GT: Well, I did, but to be honest, back when I was in school and in training, there was a lot of stigma about the field, so I started out in Neurology, because, somehow, that seemed to be the more acceptable alternative. And, rather than being a neuropsychiatrist, I was looking at the opportunity of being a psychoneurologist. But, actually, I started my residency training in Neurology, and I really liked the academic side of Neurology, but there were, a lot of serious chronic diseases, and there was very little to offer therapeutically. And, then, I actually did develop a positive mentoring relationship with the Chairman of the Department of Psychiatry, in the program I was training. He was very encouraging that if I wanted to switch into Psychiatry he would help to facilitate that. So, the rest is history from there.

JB: What year was that that you made the switch?

GT: It was after my first year of residency training.

JB: So, where about are we now, what year was that?

GT: Calendar year?

JB: Yes.

GT: Oh, gosh, that's going to be a tough question.

JB: What year did you finish?

GT: I finished medical school in 1976, so, I guess probably around 1981, something like that.

JB: What was it you saw in Psychiatry, at that time, that made you hesitant and, then, allowed you to accept that as a career path?

GT: Well, I was always fascinated by human behavior and kind of what makes people tick and do what they do. On the other hand, I was interested in how stress and environment influenced physical health. I liked the interface between psychology as a behavioral discipline and medicine, and psychiatry specifically offered an opportunity to look at the psychosomatic interface. Of course, back then, psychosomatic medicine was a very hot topic and there was a lot of interest in it. So, that was really the magnet, I think. I was interested in the areas of the brain that were involved, or at least we thought were involved in regulating behavior and I found the biological aspect of psychiatry to be very attractive. What kept

me, as I said earlier, from initially getting into psychiatry was really the stigma. At least, in my training program, it was great if you were going to go and be an orthopedic surgeon, or it was great if you wanted to go out into the community as a family practitioner, but psychiatry was seen as just a lot of those weirdoes. There weren't a lot of extremely positive role models within the program of psychiatry, so it was something that you didn't necessarily feel proud to talk about to others that I'm going to do, as my specialty training; whereas, in Neurology, particularly at Minnesota at that time, there were some extremely strong personalities who were leading that department. It was one of the best, nationally. The chairperson, Dr. A. B. Baker, was a classic figure in Neurology and had written a classic text of neurology. He was an outstanding teacher and mentor, so it was much more credible, shall we say, to be on the pathway of neurology at that point in time.

JB: Was that, in part, because the psychiatry department was psychoanalytically oriented?

GT: Yes, as well as they were family therapy focused, and certainly non-biological, at that point in time. But, I think if you look back into the 1970s and the early '80s, the field of psychiatry, for the most part, wasn't held in high esteem and by a lot of people, it was considered not to be a legitimate medical discipline. It was almost like leaving the field of medicine. So, that was an issue at first that influenced me.

JB: Do you think that's changed?

GT: Well, there are residuals of that opinion that's still out there, some of it deserved but much of it not. I think it's lessened dramatically. On the other token, I think we saw in the late 1980s and the '90s, an increase in the interest in psychiatry as a specialty. I think, to some degree, that's waning a bit. People are being lost to, either basic sciences or other disciplines. People that might have gone into psychiatry ten years ago, I think, are a little bit more reluctant, maybe, for different reasons today than they were at the time. But, nonetheless, I think there is that issue that we're not always attracting the best and the most brilliant minds into the field and I think that does have a prognostic implication for the future of psychiatry.

JB: What do you think the reservations are now about going into psychiatry?

GT: I think there is an issue about the overall credibility of the field. I do think, of course, the Decade of the Brain made a positive difference in trying to imprint a medical discipline to the field and I think psychiatry research has improved. It's a more rigorous discipline, but I think a lot of people still are just unfamiliar with the area. They have their preconceived ideas about what it means to deal with a schizophrenic patient or a depressed

patient and, perhaps, don't appreciate how rewarding the field could be. And also, probably don't see it as financially lucrative as procedurally related specialties. I think there are probably two phenomena that are interacting. It may be less attractive to go into medicine because of the regulatory environment that we see, and liability components. Some people that might have gone into medicine, I think, are going into other disciplines. And, then, within medicine, I think there's an increased reluctance to go into some of the softer disciplines.

JB: So, what happened after you did your psychiatry training?

GT: Well, I ended up staying on in an academic faculty appointment and started off in Consultation Liaison Psychiatry and, in concert, was doing some bench research. I was pursuing my PhD, in parallel, so I was working with a joint program between Pharmacology, Biochemistry and Psychiatry studying muscarinic acetylcholine receptors. We were looking at muscarinic receptors on the erythrocytes and comparing them with that within the hippocampus to see whether we could use erythrocytes as models for studying the relationship between the effect of drugs on cognition and on muscarinic receptors. So, I was doing that PhD thesis and, at the same time, doing Consultation Liaison Psychiatry. I really enjoyed it; I liked working with psychiatric problems in a medical, surgical setting.

GT: At this point, did you start to imagine that your work was going to have an overriding objective or primary goal?

GT: No, I can't say. I think what I was interested in first was writing and publishing, case reports. Rather than just focusing on one particular aspect of research, I enjoyed the diversity of looking at different kinds of issues and problems; although, I suppose the common denominator was that there was an underpinning of psychopharmacology. And, certainly over the first few years, I began to move in the area of psychopharmacological research and did a lot of translational work between the bench and the bedside.

JB: I'm just struck at the way you seemed, from the very beginning of college, to be straddling a couple of different perspectives and trying to combine them. Was that something consciously in your head at the time, or something you just felt was great?

GT: I think probably the latter. When I look back now, I think that sometimes we have a lot of artificial boundaries; we create categories. I did enjoy working across those apparent boundaries and trying to synthesize or integrate things. And, it was also challenging to work across different disciplines.

JB: When did you set up your own lab?

GT: Probably about my fourth or fifth year after training, I started following up on my PhD thesis, and started doing a fair amount of work, principally on muscarinic acetylcholine receptor activity. But, then, I also got involved in administrative matters; started doing some additional outpatient clinical research. I had some grant activity in that area. We had a multi-specialty physician practice, even though it was a university based operation. I got involved with the board of directors there, so I got into the business side early. And, eventually, something had to be given up, and it turned out to be the lab research. So, I started focusing more on clinical research and, then, got more and more into doing administrative activities, at the medical center level. But, then I also became Chairperson of our major teaching hospital. So, that took me down a business administrative route in parallel to the research while still trying to keep up with clinical care and teaching. There wasn't a lot of time left over, so the basic science piece is what got left behind, I guess.

JB: So, tell me about your clinical research at that time and what you liked about it.

GT: It was primarily pharmaceutical research. I did have some projects that we were doing that were funded federally; one of them was a classic project that Bob Prien had been involved with, looking at lithium and its' long term effects on prevention of recurrence of disease. Subsequent to that, I developed an interesting multi-center project that focused on cognitive psychotherapy, looking at cognitive therapy vs. drug vs. the combination. It was one of the first combined efforts in that area. I was working with Steve Holland, who, still, I think, is very interested in that area of research. And, we did a number of drug studies, as well. We had a diverse and fairly large clinical population and first we started working in the areas of depression, anxiety, and Alzheimer's and, then, later, in the area of schizophrenia. I enjoyed learning about the novel pharmacology of some of the molecules we were working, and learning a little bit about clinical trial methods and about regulatory environment.

JB: These were Phase III trials?

GT: Phase II and Phase III trials, principally, occasionally some Phase I trials. But, it was usually pre-approval kind of activity. And that turned out to actually be one of my early introductions to the pharmaceutical industry, which also played a major role later in my life, because I spent about fourteen years at a large pharmaceutical company in a senior role. So, you know, when you look back, these were all sort of entrees to different opportunities.

JB: When was that you did these industry funded clinical trials?

GT: It was between year five through year eight or nine after residency.

JB: In the 1980's?

GT: This was taking me into the '80s, exactly.

JB: An interesting time.

GT: Yes, and around '85, I became Chairperson of the department at a major teaching hospital while continued to try to build a research center and recruit people that had a similar mindset.

JB: Was there anything unusual about building those kinds of relationships with companies? What was it like to put yourself into that world? Were others concerned about it?

GT: To be honest, those relationships are more stigmatized today than they were back then. People at the time either had a relative disinterest or had a degree of apathy regarding the whole issue of the industry and academic interface. It was not necessarily seen as prestigious as federally funded research; I don't think that it was really on a lot of people's radar screens. In my experience it had to do with the credibility of the individual people rather than the company or the research itself. It really got down to people; there are some people that I really enjoyed working with and I had tremendous respect for and trust, and there were others that you run across where you don't have those same positive feelings. I think that has been true throughout my career in whatever area I have worked. I think we have to stay away from trying to lump and stereotype people, based on what they've done or what they're doing because a lot of it is really about the individual, a lot more than it is what organization he or she are in, per se, or what kind of discipline they're in. It's really about the person and, so, that's really been a cornerstone. I went through my career, which has had its' pluses and minuses, but I really believe strongly in the integrity of the individual.

JB: Thinking back on your early research, what's the work that you did that you're most proud of?

GT: Prior to going into the industry?

JB: Yes.

GT: I think probably it would be the offshoot from my PhD thesis we were talking about earlier, for example, the effects of lithium on muscarinic receptors and the role of acetylcholine in bipolar disorder. One that I think was really interesting, that I enjoyed a lot, was looking at the effects of chronic alcoholism on cholinergic activity, and, in fact, showing that younger chronic alcoholics had some of the same decrements that you saw in Alzheimer's patients, suggesting that alcohol, as a toxin, was prematurely inducing a senescence, a cholinergic senescence, so to speak. And, so, I found those kinds of projects quite interesting and I felt good about them. But at that point, being in a relatively small medical center

I also realized that a lot of the work that I could do was influencing on a small scale. One of the opportunities that I saw was the chance to make a much bigger difference on a much, much broader scale and that was to take the big risk to leave an academic position and a department chair to go into a drug company, which, at that time, to some degree, was the dark side for a career.

JB: And, tell me more about what was risky about it.

GT: Well, giving up the image of being an academic psychiatrist, and academic researcher to go into the pharmaceutical industry - which was not necessarily always viewed as research that was done at the same level of rigor, integrity, objectivity - that also turned out to be a challenge. And the challenge was to build a neuroscience research program within a large pharmaceutical company that could be respected for the quality of the people and the integrity of the work that was being done. And that really was a lot of what I did through the '90s, when I joined Eli Lilly and Company and went into the neuroscience division, eventually leading the neuroscience division.

JB: Did you worry that you wouldn't be able to go back into academy?

GT: Yes, so what I did was to "cheat". I took a leave of absence from my academic position for a year. There were times I was close to going back for a variety of reasons, but I'm glad I stuck it out although, I think there is the opportunity to move back and forth, and subsequently, other people have shown that you can do that. You can go bi-directionally as long as you keep up the credibility of the research you're doing and the relationships. You know, you can go back and forth and there's no reason you shouldn't be able to. There shouldn't be a barrier. But when you're first doing it, especially, when you were part of an earlier generation of academic researchers, you have that concern about whether or not you'd be able to go back if you wanted to go back. And the longer you're in the industry the harder it is, I think, to go back, and that was certainly a concern.

JB: Is there something that companies or the NIH or academic centers should do to make that easier to go back and forth?

GT: Yes, the more the two come to the realization that they are partnering and working together they can serve the greater good in a much more effective manner. I think a lot of it is sort of artificial barriers and perceptual barriers that really harm reality. You know, there's always a lot of lip service about a private-public partnership when it comes to research, but with a few exceptions, it's been hard to put that into practice and see it operating on a larger scale. So, there still isn't as much interchange across fertilizations that I think there could be. I think the college here is an example where there's still a struggle trying to understand the role

of industry, but, more specifically, the role of industrial scientists. So that issue plays into the ability to be perceived with credibility and move back and forth. It is doable, but it takes work, I think. So, ideally, going forward, I think it would be important to have a better understanding by both sides and a greater effort to truly partnering in research. And looking forward, I think, the economics are going to demand that there be more synergy and less redundancy.

JB: Do you think science is done differently in industry or that industry scientists are different, in any important aspect from scientists in the academy?

GT: Ideally, no. Based upon my experience at Lilly in the 1990s, I think the quality of the science, the rigor of the science is perhaps greater in the industry, because one had to overcome some of the stigma when it came to publishing and because it's a regulated industry. You know, people can end up in jail, which is not necessarily the case in academia. So, when it came to the rigorous statistical analyses and the rigor of maintaining a good double-blind design, I think the quality of the work done by industry often was, at least, as good as, and often surpassed what you might see coming out of an academic center. I think it was always perceived that way. Part of the problem was that there was also some Phase IV research done by the industry that probably didn't have that level of rigor and appeared to have bias in it. And that research creates an image that taints a lot of the more impressive phase II research or even preclinical research that goes on within the industry. I think that some of that work is really impeccable science in the industry and extremely well thought out; the risk and the reward are so big and on such a large scale that one can't afford to make big mistakes.

JB: I don't know if you have an example from the time you were at Lilly, about the kinds of misperceptions that came up about what you were doing or what your department was doing, or something that needed to be mend?

GT: One of the first issues that I had to deal with, which is somewhat related, is the issue of antidepressants and suicidality, which, interestingly, is back on the plate now from a child adolescent perspective. In the early '90s, based on some academic case reports, anecdotal uncontrolled observations, this whole issue, that antidepressants induced suicidality, gained tremendous momentum. Part of the issue, initially, was the belief that the pharmaceutical industry wouldn't and couldn't pursue a credible objective evaluation because they're biased and they are in conflict because of the commercial sales of these products. So, one of the great challenges for us was taking a leadership role in this case at Lilly, and to put together very objective analyses of well controlled prospective double-blind databases to really address the hypothesis. It was a hypothesis that really

had to be addressed with significant scientific rigor and using double-blind methodology. Obviously, as you well know, suicidality is part of depression, and so, when someone who is depressed and becomes suicidal, it could well be the disease. So the question was how to separate the natural course of the disease from a theorized iatrogenic cause that antidepressants induced suicidality. I think the double-blind methodology was the key. While it's not without some critique, I think it is the best thing that we have to offer in the field. The other thing was being able to pool lots of data from lots of different sources so that the sample size was large enough to eliminate some potential biases. And, we presented the data and worked with the FDA and the Neuropharm Advisory Committee. And, I think that made a major difference, because there was a time when antidepressants, could have been taken off the market or certainly could have had profoundly restrictive labeling. That, I think, would have been to the detriment of patients. Even without it in many cases, patients stopped their medication without talking to their physician and got into clinical trouble relapsing and, even, in fact, becoming suicidal due to the disease. So, there was a bias to try to overcome. These questions can be addressed with appropriate scientific rigor by the industry. But, again, it falls back on individuals. You had to have the commitment and integrity and the support to pursue that.

JB: When you were trying to manage that, who, helped to figure out how to make your case?

GT: One of the things I felt good about my legacy with industry, was of being able to come up with some ways to test this question, by leveraging a large existing database. What made that more successful in bringing it to fruition was a combination of partnering with the right academic consultants who could bring in additional perspectives and having a very talented internal group to operationally carry out a lot of that work, whether it was statistics or clinical development, or whatever. It had to be a team approach and we had a very good internal team, which is essential to be successful. It was complimented by that consulting academic outside perspective that could enrich the discussion and the analysis of data. Last, but not least, you can't do this in any environment unless you have supportive management. The management team, if they support it can make it happen. When they don't support it and don't believe strongly in it, that's when it doesn't necessarily happen with the same degree of rigor and that's when some of the stereotypes that we were talking about earlier can emerge. Fortunately, I think, at that point in time of my career, there was very strong interest in letting the science answer the question and let the commercial ramifications fall where they may. But, the

important thing was scientifically addressing the question and coming up with the right answer.

JB: Do you have an idea why the issues and concerns about suicidality came and went and then came back?

GT: Why is it back? I think that one of the problems is that we have not come up with more sophisticated ways to assess suicidality. It's still often based on crude observations. And, one has to look at the data with significant rigor. My understanding of the child and adolescent database where the renewed interest originated from is that, there were no fatalities in that database. Yet, it's perceived that when we're talking about suicide it must be that people are dying. Secondly, a lot of the activities which were not necessarily self-directed aggression in sense of fatality or high risk of mortality were lumped together with intentions. And, if all got lumped together as suicidality and when you look at those data, you saw things that were suggestive of a trend. But, when you really look at the data and dissect it apart I don't think there's a signal there. The bottom line to your question, why did it happen is, that we still don't look at adverse events and, specifically, we don't look at suicidality in a sophisticated way and we don't use good clinical skills often to categorize or describe things.

JB: I wondered if you had thoughts about what psychopharmacology could do to better communicate what the field is to the public.

GT: Yes and that's what the Decade of the Brain was going to be about when Congress supported it in the '90s. But, I think it never really quite came to fruition. I don't think the media found the story to be as sexy and as interesting as one would like it, so the tendency was to cover the more sensational, negative, anecdotal things about mental health and not to put the effort into trying to educate people on understanding the brain. And, as long as the media doesn't perceive that to be an interesting and worthy topic, people are going to continue to be relatively ignorant about it. I think that if people are only influenced by movies where they see somebody's bizarre behavior, they would generalize that to an entire understanding of psychiatry. So, it's all based on negative anecdotes. I don't think there has been a concerted effort to really try to educate people. And, to some degree, the media has to accept some responsibility for that, because they haven't seen that as interesting. Where else can people get information other than the media anymore? The media does dictate what we know, what we think, or what we don't know. So, until we have a very strong collaborative campaign to try to educate people about mental health, the role of the brain and behavior, I see little change, unfortunately.

JB: OK, tell me about your decision to leave Lilly and do other things.

GT: I had a chance to have a lot of different experiences there, all the way from pre-clinical evaluations of compounds and prioritization of strategic planning to move human testing through all the phases of drug development. I also had experience to commercialize a product as a product president, which was to oversee the entire global neuroscience portfolio from clinical to commercialization, working on a global basis with international colleagues. So, the great thing was that I had a chance to do lots, lots and lots of things. The bad part was that as in any large environment, and with the changes that have gone on, it was getting more and more bureaucratic, and I felt it was harder and harder to get things done in a timely way; management was less and less receptive to innovation and more and more oriented to risk aversion. I felt it was time to do some things on my own and see if I could, in that environment, recapture some creativity to do some more novel things that I think I had a chance to do through the early '90s. But by, certainly, 2000 – 2003 that was much, much harder to do in a large pharma environment. That made me interested in the biotech world, which is where I am now in. the third phase of my career.

JB: It was interesting the way you described your work at Lilly; that you could see all the way through from basic science out to global markets and think about from creating a product and distributing it. I imagine that was particular to your position. Are many people in companies who could have an eye on the full array all the way going?

GT: Yes, although they may not get a chance to do it first hand, but there is an opportunity for many to see the big picture, because you can't do your work effectively without a longer term vision and a strategic plan. Then, again, you also have to learn about implementation and the operational part of it, because it's great to have a vision but if you're not able to implement it you're never going to get anywhere. So, you've got to have that effective plan to implement, as well.

JB: A little bit different than academia.

GT: Yes. Well, I think, there's certainly a much longer range vision in what you're doing and on a much larger scale, and with a much greater complexity. The international aspect of it is just one example of complexity that one deals with. So, it is definitely a team effort and you have to have people from lots of different disciplines, probably in a sense, not unlike as in a psychiatric unit where you bring people from different disciplines together. But in industry of course this is on a much bigger scale with people not only from medical and healthcare disciplines, but also other disciplines outside of medicine. The fun part of it is that it's very much

team dependent. On the other hand, it also lends itself to creating a lot of bureaucracy, checks and balances, committees and things when you've got that many different people involved as decision makers. You lose a sense of one person being empowered and accountable, which is something that I've been able to recapture now.

JB: So, what kind of innovation and creativity were you interested in?

GT: Well, initially, it was more just trying to leverage my experience as a consultant and be able to take the experiences I had, and help people that are in a start up phase; help them be more efficient, let's say, in getting from point A to point B. But, because of my background, I started to helping them to look at the overall management and the direction of a company, not only on its science, but also on its' financing and developing relationships, etc. And, then, with one of the particular companies, the opportunity to be CEO opened up, and I was recruited. It's a company that is focused on some very novel pre-clinical science on the hypothalamus and looking at understanding appetite and satiety mechanisms and why when you first lose weight there's a tendency to regain. And, I really enjoyed it. It was a chance to get into to some really interesting neuroscience. It was also a new area for me and it was very stimulating to learn about obesity, and also of making it a business. We were operating in a business model; taking existing molecules, screening them and putting them together. And I became, overtime, an advocate of combining medications. The reality is, if you go out and look at clinical practice, more often than not, people do combine medications and what that says is, that existing drugs really are inadequate in achieving response and remission for a large number of people. Clinicians, obviously, in their own intuitive way, are trying to find combinations that will give them better outcomes. So, we're combining certain unique drugs to provide longer term sustained weight reduction. And, that's been fun. .

JB: Well, obviously, you've found a lot of advantages to being able to work in companies and do science toward creating a product. Do you think there is any drawback for increasing cooperation and partnership between academics and companies?

GT: No, not really. I think that some people might think there are drawbacks because of "commercial bias". I think industry is becoming increasingly transparent because it's required to. I think, in academia, there is a way to go to get there yet. I don't think the ethics in being an industry scientist need to be different than the ethics of being an academic researcher. There should be a single set of ethics that are applied to anyone doing research.

- JB: There is a concern that academic science is less and less transparent, and that open communication is less common in the academic circle.
- GT: Yes, and the more people have tried to deal with conflict of interest, the more people find ways to circumvent it.
- JB: I am wondering how you balanced your professional and personal life; do you have any tricks?
- GT: No. I wish I had. . I think that is a major challenge. People talk about work - family balance, talk about how important it is, but very few of us, does it effectively. And, I certainly wouldn't put myself forward as the ideal template for that. As you do get older you do look back and you see where, a lot of times your balance was towards work and less towards family and you'd like to go back and rebalance that and, you know, you can't. One of the reasons I left industry, that we didn't talk about, was that I wanted to have more free time to, either, do the things I wanted to do, personally, and/or things around family that I didn't spend as much time at.
- JB: You were doing a lot of interesting things; what has been, for you, the most exciting kind of thing that you've gotten to do in your career?
- GT: The drug industry, as a research venue, for the most part is relatively fragmented. I mentioned earlier the complexity of trying to pull together people from many, many different disciplines in order to make decisions, move projects forward. There was a paradigm that was developed by a Harvard business professor to pull things together by so-called, "Heavyweight Teams". It was used in the auto industry and computer industry, but hadn't been used in the pharmaceutical industry until in the mid-90s Lilly opted to try that model. In a Heavy Weight Team, a single leader brings people from all these different disciplines together. .Everyone reports on a particular project to that leader instead of their respective home bases. We did this with a demonstration project for the development of Zyprexa (olanzapine) and I got to be selected as the leader for that Heavyweight Team. We were able to develop Zyprexa and launch it with a very strong package and lifecycle plan in a fairly short order. The drug became a very large commercial success, and it changed the lives of many, many people. And, that, looking back, was a tremendously rewarding experience. Rather than people coming in and saying, "I'm a statistician" or, "I'm a toxicologist,".people would come in and say, "I'm working on Zyprexa to help treat schizophrenia". There was an enthusiasm and excitement. But one of the problems within the pharmaceutical industry is that it's much like a pendulum and models and things change, go back and forth, back and forth, and, so, just about all that was good in this model, to a large degree, has been somewhat disassembled. But it was a great experience.

- JB: It's really interesting.
- GT: There was a vision and a common purpose, but it also points out the value of a positive work environment. You can be doing interesting research, but if you're not in a work environment that you're happy about or you don't have the collegial interaction that's stimulating, then, you lose a lot. So, it's not just the work you're doing, but the environment that you're doing it, I think makes a difference. So, that was the ideal time; it was a great exciting project in a tremendously stimulating work environment with a lot of really talented people that were highly energized and motivated to make this happen.
- JB: Ultimately, it was very successful.
- GT: Yes.
- JB: Can you think of the thing that you liked the least about your work what you've done in your career?
- GT: Maybe the political side of the business. You see a lot of people who are very political and that is a way to move ahead in our environment. It's where society is. But, that's something I've just never been motivated for. I don't find it particularly rewarding. I think there's a fundamental interplay of what you know and who you know and I've always been uncomfortable with the people that don't know a lot of what, but know a lot of who's and that can sometimes be, for example, within the pharmaceutical industry, a way to be successful.
- JB: Are there other important things that we haven't talked about that you'd like to talk about?
- GT: Well, you're assuming that what we've talked about is important. I don't think so.
- JB: Are you sure?
- GT: I think maybe one thing that I would like to end with: and that is about future. I think the future of psychiatry and psychopharmacological research is at a kind of crossroads. A lot of the enthusiasm about the early discoveries in neuroscience has waned, because we haven't really been able to translate some of that into clinically meaningful information. A guy had raised the question how many articles have you read over the last two to three years in the *American Journal of Psychiatry*, or the *Archives of General Psychiatry* that changed the way you practice medicine, and the answer of the vast majority is: "zero". That is the issue. That is the issue: our research is not making as much of an impact on improving the quality of care and dealing with unmet needs we have in the field as it should. And, that's one of the challenges that we face going forward, to make research more relevant for clinical care. I do think that does come through translational work. I think our colleagues in oncology have done

a nice example of making that happen. Everybody is sort of shifting and placing their bets now on cancer and oncology products. That is a hot area and neuroscience and psychiatry is becoming less and less interesting as a target for research. So, let's just look forward and say that the drug industry, by and large, significantly reduces the funding for research into psychiatric disease ten years from now; what is that going to mean for the College and for the people working in neuropsychopharmacology? I think there are some issues that are really going to be quite challenging for us.

JB: That's great. Good. Thank you.

GT: Good enough.

JB: Thanks a lot.

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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.

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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 each of the first seven volumes in this series interviewees tell the story of neuropsychopharmacology from a different perspective, reflecting the development of the field from the vantage point of researchers involved in one or another area of research. Volume Eight does not focus on any particular area of research; interviewees talk about contributions to diverse topics and the volume as a whole mirrors the changes that have taken place in the entire field in fifty years time. Volume Eight also differs from the other volumes by its Preface. In all other Volumes the Preface provides background information to interviewees' research contributions, placing the contributions into a historical context, whereas in the Preface to this Volume the larger framework of the development in neuropsychopharmacology is discussed. Dedicated to the Memory of Milton Greenblatt, President ACNP, 1964, Volume Eight is edited by Carl Salzman, a distinguished leader of education in neuropsychopharmacology, Salzman was instrumental in opening up research with psychotropic drugs in the aged.